



THE  
AMERICAN JOURNAL  
OF THE  
MEDICAL SCIENCES

E. B. KRUMBHAAR, M.D.  
EDITOR

WILLIAM C. STADIE, M.D.  
ACTING ASSOCIATE EDITOR

NEW SERIES

VOL. 210



LEA & FEBIGER  
PHILADELPHIA  
1945



COPYRIGHT  
LEA & FEBIGER  
1945

PRINTED IN U. S. A.

# CONTENTS OF VOL. 210

## ORIGINAL ARTICLES

### No. 1—JULY

- Penicillin in the Treatment of Pneumococcal, Meningococcal, Streptococcal and Staphylococcal Meningitis. By WILLIAM L. WHITE, M.D., FRANKLIN D. MURPHY, M.D., JOHN S. LOCKWOOD, M.D., and HARRISON F. FLIPPIN, M.D. . . . . 1
- Infective Hepatitis. With Special Reference to Prognosis. By J. BASIL RENNIE, M.D., M.R.C.P. With the technical assistance of T. G. PIRIE . . . . 18
- Oral Administration to Volunteers of Feces From Patients With Homologous Serum Hepatitis and Infectious (Epidemic) Hepatitis. By CAPT. JOHN R. NEEFE, M.C., A.U.S., JOSEPH STOKES, JR., M.D., and JOHN G. REINHOLD, PH.D. . . . . 29
- Lymph Nodes in Leishmaniasis. Report on 2 Cases. By LT. COL. D. M. ANGEVINE, M.C., A.U.S., CAPT. T. R. HAMILTON, M.C., A.U.S., CAPT. F. G. WALLACE, SN.C., A.U.S., and LT. COL. J. B. HAZARD, M.C., A.U.S. . . . . 33
- Mite or Scrub Typhus. A Clinical and Laboratory Study of 64 Cases. By MAJ. THOMAS E. MACHELLA and LT. COL. JAMES S. FORRESTER . . . . 38
- On the Toxicity of Streptothricin. By GEOFFREY RAKE, M.D., B.S., DOROTHY HAMRE, PH.D., FREDERICK KAVANAGH, PH.D., WALTER L. KOERBER, PH.D., and RICHARD DONOVICK, PH.D. . . . . 61
- Klebsiella Pneumoniæ Bacteremia Successfully Treated by Penicillin. By COMD'R J. LESTER KOBACKER (MC) USNR, and LT. COMD'R G. BURCH MEHLIN (MC) USNR . . . . . 66
- Ricketts in Iceland. By NIELS DUNGAL, M.D. . . . . 70
- Hemorrhagic Telangiectasia With Pulmonary Artery Aneurysm: Case Report. By R. WAYNE RUNDLES, PH.D., M.D. . . . . 76
- Tiselius Electrophoresis Studies of Plasma Proteins in Addison's Disease. By E. PERRY McCULLAGH, M.D., and L. A. LEWIS, PH.D. With the technical assistance of JAMES CLARK, A.B. . . . . 81
- The Incidence, Causes and Intermittency of Proteinuria in Young Men. By IRVING J. WOLMAN, M.D. . . . . 86
- Electrocardiographic Changes Associated With Lesions in the Deeper Layers of the Myocardium. An Experimental Study. By RAYMOND D. PRUITT, M.D., ARLIE R. BARNES, M.D., and HIRAM E. ESSEX, PH.D. . . 100

### No. 2—AUGUST

- A Comparison of the Behavior of Microcrystalline Sulfadiazine with that of ordinary Sulfadiazine in Man. By JOHN G. REINHOLD, PH.D., FRED. J. PHILLIPS, M.D., and HARRISON F. FLIPPIN, M.D. With the technical assistance of LILLIAN POLLACK . . . . . 141

Penicillin—Its Present Status in the Treatment of Infections. The Nathan Hatfield Lecture XXIX. By CHESTER S. KEEFER . . . . .	147
A Study of the Types of Hypersensitivity Induced by Penicillin. By ADOLPH ROSTENBERG, JR., M.D., and HENRY WELCH, PH.D. . . . .	158
Effect of Sodium Salicylate on the Sedimentation Rate of Erythrocytes <i>in Vitro</i> . By F. HOMBURGER, M.D. . . . .	168
The Erythrocyte Sedimentation Rate in Rheumatic Fever. Its Significance in Adolescent and Overweight Children. By T. N. HARRIS, M.D. . . . .	173
Experiments on Components A and B (Quick) of Prothrombin. By WILLIAM J. O'NEAL, M.D., and CONRAD R. LAM, M.D. . . . .	181
Hemolytic Transfusion Reactions Due to the Rh Factor. Report of 2 Cases. By CAPT. ARTHUR W. FRISCH, M.C., A.U.S. . . . .	184
The Acceptability and Effectiveness of the Condom as a Contraceptive Method. By CHRISTOPHER TIETZE, M.D., and JOHN B. HAGAMAN, M.D. . . . .	189
The Magnesium Partition in Hyperthyroidism. With Special Reference to the Effect of Thiouracil. By GROSVENOR W. BISSELL, M.D. . . . .	195
Vitamin Levels in Sprue. By DAVID CAYER, M.D., JULIAN M. RUFFIN, M.D., and WILLIAM A. PERLZWEIG, PH.D. . . . .	200
Early Filariasis (Bancrofti) in American Soldiers. By CAPT. IAN G. HODGE, M.C., A.U.S., CAPT. ERIC DENHOFF, M.C., A.U.S., and LT. COL. JOSEPH B. VANDER VEER, M.C., A.U.S. . . . .	207
Tularemia Pneumonia. Review of American Literature and Report of 15 Additional Cases. By BYRON M. STUART, M.D., and ROSCOE L. PULLEN, M.D. . . . .	223
Osteomyelitis Caused by Granuloma Inguinale. Report of a Case With Cultivation of the Donovan Body in the Yolk Sac of the Developing Chick Embryo. By WALTER H. SHELDON, M.D., BEN R. THEBAUT, M.D., ALBERT HEYMAN, M.D., and MARGARET J. WALL . . . . .	237
Hemochromatosis Associated With Primary Adenocarcinoma of the Liver. A Case Illustrating Diagnostic Features. By J. A. OSHLAG, M.D., and R. F. MARTIN, M.D. With pathologic report by C. H. BINFORD, M.D. . . . .	245

### NO. 3—SEPTEMBER

Adrenalin Administration in Persistent Anxiety States. By D. EWEN CAMERON, M.D. . . . .	281
Eosinophilic Lung (Tropical Eosinophilia). By LT. COL. PHILIP J. HODES, M.C., A.U.S., and COL. FRANCIS C. WOOD, M.C., A.U.S. . . . .	288
Laryngeal Edema, Myocarditis and Unexpected Death (Early Acute Laryngotracheobronchitis). By OTTO SAPHIR, M.D. . . . .	296
The Life Cycle of the Erythrocyte After Splenectomy and the Problems of Splenic Hemolysis and Target Cell Formation. By KARL SINGER, M.D., and LEO WEISZ, D.V.M. . . . .	301
General Acquired Anhydrosis. By HUGO T. ENGELHARDT, M.D., and J. P. MELVIN, JR., M.D. . . . .	323

Poisoning by Hydroquinone and Mono-methyl- <i>paraminophenol</i> Sulfate. Report of 2 Cases With Autopsy Findings. By CAPT. IRVING ZEIDMAN, M.C., and CAPT. RUDOLF DEUTL, M.C. . . . .	328
The Xiphosternal Crunch and Its Incidence in Healthy Inductees. By MYER SOLIS-COHEN, M.D. . . . .	333
A Heredofamilial Neurologic Disease, Resembling Charcot-Marie-Tooth Type of Progressive Muscular Atrophy, in a Chinese Family. By MAJOR CALVIN F. KAY, M.C., and MAJOR HERBERT S. GASKILL, M.C. . . . .	342
A Study of the Goitrogen, Promizole, With Reference to the Thyroid, Metabolism and the Blood. By GEORGE M. HIGGINS, PH.D. . . . .	347
Interference Between Inactive and Active Viruses of Influenza. III. Cross-interference Between Various Related and Unrelated Viruses. By WERNER HENLE, M.D., and GERTRUDE HENLE, M.D. . . . .	362
Interference Between Inactive and Active Viruses of Influenza. IV. The Nature of the Interfering Agent. By GERTRUDE HENLE, M.D., and WERNER HENLE, M.D. . . . .	369
Methionine in the Treatment of Toxic Hepatitis. By JAMES H. EDDY, JR., M.D. . . . .	374

## No. 4—OCTOBER

Studies on Streptomycin in Man. 1. Absorption, Distribution, Excretion and Toxicity. By HAROLD A. ZINTEL, M.D., HARRISON F. FLIPPIN, M.D., ANNA C. NICHOLS, MARJORIE M. WILEY, and J. E. RHOADS, M.D. . . . .	421
Case of Streptococcus Viridans Pneumonia Successfully Treated With Penicillin. By MAJOR SAUL SOLOMON, M.C., A.U.S. . . . .	431
Observations on the Continuous Intramuscular Method of Administering Penicillin. By HAROLD L. HIRSH, M.D., and HARRY F. DOWLING, M.D. . . . .	435
Electrocardiographic Observations in Normal Thyroidectomized and Thiourea Treated Rats. By ROBERT K. WALLER and HARRY A. CHARIPPER. With the technical assistance of ALBERT H. STENGER . . . . .	443
A Study of the Relationship of the Basal Body Temperature to the Basal Metabolic Rate in Hospitalized Patients. By CAMPBELL MOSES, M.D. . . . .	453
The Danger of Continued Arsenotherapy in Cases of Erythema of the Ninth Day. By MAJOR WILLIAM LEIFER, M.C., A.U.S. . . . .	458
Possible Effectiveness of the L. Casei Factor ("Folic Acid") Concentrates on Refractory Anemia and Leukopenia, With Particular Reference to Leukopenia Following Radiation Therapy. By C. J. WATSON, W. H. SEBRELL, J. L. MCKELVEY, and F. S. DAFT. With the technical assistance of VIOLET HAWKINSON . . . . .	463
Synchronization of Neurotic Behavior Patterns. By EDMUND BERGLER, M.D. . . . .	470
Atrial Septal Defect. Study of Hemodynamics by the Technique of Right Heart Catheterization. By EMMETT S. BRANNON, M.D., H. STEPHEN WEENS, M.D., and JAMES V. WARREN, M.D. . . . .	480
Idiopathic (?) Hypoprothrombinemia. Report of a Case. By V. THOMAS AUSTIN, M.D., and HENRY QUASTLER, M.D. . . . .	491

Aplastic Anemia Terminated by Removal of a Mediastinal Tumor. By GEORGE H. HUMPHREYS, II, M.D., and HAMILTON SOUTHWORTH, M.D.	501
Use of a Simple Postural Test in Neurocirculatory Asthenia. By MAJOR W. A. JEFFERS, M.C., A.U.S., CAPT. S. C. SHEIMAN, M.C., A.U.S., and LT. COL. G. H. O'BRASKY, M.C., A.U.S.	511
Salmonella Appendicitis. By A. DANIEL RUBENSTEIN, M.D., and BEN B. JOHNSON, M.D.	517

## No. 5—NOVEMBER

Homologous Serum Hepatitis and Infectious (Epidemic) Hepatitis, Experimental Study of Immunity and Cross Immunity in Volunteers. A Preliminary Report. By CAPT. JOHN R. NEEFE, M.C., A.U.S., JOSEPH STOKES, JR., M.D., and CAPT. SYDNEY S. GELLIS, M.C., A.U.S.	561
Streptomycin: Absorption, Diffusion, Excretion and Toxicity. By DOROTHY H. HEILMAN, M.D., FORDYCE R. HEILMAN, M.D., H. CORWIN HINSHAW, M.D., DONALD R. NICHOLS, M.D., and WALLACE E. HERRELL, M.D.	576
The Antagonism of Local Anesthetics against the Sulfonamides. By BURNHAM S. WALKER, M.D., PH.D., and MATTHEW A. DEROW, M.D., PH.D.	585
The Penetration of Penicillin into Joint Fluid following Intramuscular Administration. By CAPT. VICTOR G. BALBONI, M.C., A.U.S., FIRST LIEUT. IRVING M. SHAPIRO, SN.C., A.U.S., and MAJOR DAVID M. KYDD, M.C., A.U.S.	588
Typhoid Bacilluria and Urolithiasis. By F. DREYFUSS, M.D., and J. ROTH, M.D.	591
Human Infection with <i>Bacterium Necrophorum</i> . By CAPT. I. J. GREENBLATT, SN.C., A.U.S., and A. P. GREENBLATT	596
Unilateral Diaphragmatic Flutter. By R. HARRIS, M.D., and D. SCHERF, M.D.	598
Intestinal Lipodystrophy (Lipophagia Granulomatosis or Whipple's Disease). By HARVEY J. AMSTERDAM, M.D., and DAVID M. GRAYZEL, M.D., PH.D.	605
Stevens-Johnson Syndrome (Eruptive Fever with Stomatitis and Conjunctivitis). By MAJOR SIMON KOVE, M.C., A.U.S.	611
Experiences with 2350 Blood Transfusions at an Army General Hospital in India. By CAPT. CHARLES K. KIRBY, M.C., A.U.S.	623
A Simple Technique of Sternal Marrow Biopsy for Spreads and Sections. By ELIZABETH MERTENS, M.D.	630
The Effect of Vitamin K <sub>1</sub> Oxide upon the Anticoagulant Properties of Dicumarol. By CHARLES S. DAVIDSON, M.D., C.M., JOHN H. FREED, M.D., and HARRIET MACDONALD, B.S.	634
Final Note on a Reported Case of Erythremia, Gout and Subleukemic Myelosis. By GEORGE H. REIFENSTEIN, M.D.	638
Periarteritis Nodosa. A Case with Autopsy. By LT. COL. RICHARD N. WASHBURN, M.C., A.U.S., and MAJOR THOMAS O. OTTO, M.C., A.U.S.	640

Calcific Aortic Valvular Stenosis. By LAWRENCE H. SOPHIAN, M.D. . . .	644
A Tentative Test for Pheochromocytoma. By G. M. ROTH, Ph.D., and W. F. KVALE, M.D. . . . .	653
A Study on the Prevention of Mumps Orchitis by Gamma Globulin. By CAPT. SYDNEY S. GELLIS, M.C., A.U.S., LT. COL. AIMS C. MCGUINNESS, M.C., A.U.S., and CAPT. MICHAEL PETERS, M.C., A.U.S. . . . .	661

## No. 6—DECEMBER

Convalescence from Surgical Procedures. I. Studies of the Circulation Lying and Standing, of Tremor, and of a Program of Bed Exercises and Early Rising. By ISAAC STARR, M.D., and ROBERT L. MAYOCK, M.D. . . .	701
Convalescence from Surgical Procedures. II. Studies of Various Physio- logic Responses to a Mild Exercise Test. By ISAAC STARR, M.D., ROBERT L. MAYOCK, M.D., and MARJORIE G. BATTLES . . . . .	713
Coarctation and Acute Dissection of the Aorta Associated with Pregnancy. By THOMAS D. KINNEY, M.D., R. EMERSON SYLVESTER, M.D., and SAMUEL A. LEVINE, M.D. . . . .	725
Combined Acute Vascular Lesions of Brain and Heart. A Clinical-Patho- logic Study of 15 Cases. By GEORGE A. RACE, M.D., and JAMES R. LISA, M.D. . . . .	732
The Relationship between Cells and Plasma in Cultures of the Buffy Coat from Human Blood. By GEORGE DRAPER, CYNTHIA PIERCE and C. W. DUPERTUIS . . . . .	738
Choriocarcinoma of the Testicle. By A. J. GILL, M.D., G. T. CALDWELL, M.D., and J. L. GOFORTH, M.D. . . . .	745
Hydrometrocolpos in Infancy—A Cause of Urinary Retention, Intestinal Obstruction and Edema of the Lower Extremities. By PAUL MORRIS, M.D. . . . .	751
The Use of Penicillinase in Cultures of Body Fluids Obtained from Patients under Treatment with Penicillin. By HARRY F. DOWLING, M.D., and HAROLD L. HIRSH, M.D. . . . .	756
Incidence of Respiratory Infections following Attack by Primary Atypical Pneumonia is Unchanged. By PAUL A. LEMBCKE and LAWRENCE E. YOUNG . . . . .	762
Infectious Mononucleosis. An Analysis of 26 Clinical and 340 Subclinical Cases. By CAPT. RAY VANDER MEER, M.C., A.U.S., LT. COL. CHARLES H. LUTTERLOH, M.C., A.U.S., and CAPT. JEAN PILOT, M.C., A.U.S. . . .	765
A Comparison in Man of Sulfathiazole and 2-Sulfanilyl-3-5 Dihydrothiazole (Sulfathiazoline, Sulfahydrothiazole). By HARRISON F. FLIPPIN, M.D., JOHN G. REINHOLD, Ph.D., LEON SCHWARTZ, M.D., and ALBERT H. DOMM, M.D. . . . .	775
Treatment of Hyperthyroidism with a Combination of Iodine, Thiourea in Small Doses, and Desiccated Thyroid. By THADDEUS S. DANOWSKI, M.D., EVELYN B. MAN, Ph.D., and ALEXANDER W. WINKLER, M.D. . . .	777
Protest. A Recorded Psychiatric Program. By MAJOR ALBERT A. ROS- NER, M.C., A.U.S. . . . .	782

## NEW BOOKS AND NEW EDITIONS

Book Reviews and Notices . . . . .	135, 269, 555, 688, 812
New Books . . . . .	139, 279, 420, 558, 698, 819
New Editions . . . . .	140, 280, 420, 559, 699, 821

## PROGRESS OF MEDICAL SCIENCE

MEDICINE . . . . .	114
Bronchial Asthma: Some Problems in Differential Diagnosis. By W. A. SODEMAN, M.D.	
NEUROLOGY AND PSYCHIATRY . . . . .	125
The Amytal Interview. By BRIG. GEN. W. LEE HART, U.S.A., COL. FRANKLIN G. EBAUGH, M.C., A.U.S., and CAPT. DAVID W. MORGAN, M.C., A.U.S.	
SURGERY . . . . .	252
Wounds of the Heart. By M. H. BLAU, M.D.	
OPHTHALMOLOGY . . . . .	262
Drusen (Hyaline Bodies) of the Optic Disk. By H. P. WAGENER, M.D.	
PATHOLOGY AND BACTERIOLOGY . . . . .	381
The Pathology of the Pancreas in Experimental Diabetes Mellitus. By G. LYMAN DUFF, M.A., M.D., Ph.D.	
PREVENTIVE MEDICINE AND EPIDEMIOLOGY . . . . .	397
An Epidemiologic Approach to the Study of the Biochemical Mechanism of Motor Neuron Disease—Landry's Paralysis. By W. LLOYD AYCOCK, M.D., and GEORGE E. FOLEY	
DERMATOLOGY AND SYPHILOLOGY . . . . .	524
Biologic False Positive Reactions to the Tests for Syphilis. By HERMAN BEERMAN, M.D.	
OTO-RHINO-LARYNGOLOGY . . . . .	548
Cancer of the Mouth: Its Present-day Treatment. By WALTER MAYNE, M.D.	
THERAPEUTICS . . . . .	665
The Pharmacology and Therapeutic Applications of Anti-thyroid Com- pounds. By WALTER F. RIKER and W. CLARKE WESCOE	
RADIOLOGY . . . . .	681
Fibrocystic Disease of the Pancreas. By DAVID G. PUGH, M.D.	
GYNECOLOGY AND OBSTETRICS . . . . .	787
Uterine Bleeding and Extragenital Disturbances. By IRVING L. FRANK, A.B., M.D., M.Sc.D.	
PEDIATRICS . . . . .	798
Congenital Hemolytic Anemia: A Review of Progress. By IRVING J. WOLMAN	
PHYSIOLOGY: . . . . .	
Proceedings of the Physiological Society of Philadelphia . . . . .	131, 808

# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JULY, 1945

## ORIGINAL ARTICLES

### PENICILLIN IN THE TREATMENT OF PNEUMOCOCCAL, MENINGOCOCCAL, STREPTOCOCCAL AND STAPHYLOCOCCAL MENINGITIS\*

By WILLIAM L. WHITE, M.D.†

FELLOW, HARRISON DEPARTMENT OF SURGICAL RESEARCH

FRANKLIN D. MURPHY, M.D.†

HENRIETTA HECKSCHER FELLOW IN MEDICAL RESEARCH

JOHN S. LOCKWOOD, M.D.†

ASSISTANT PROFESSOR OF SURGICAL RESEARCH

AND

HARRISON F. FLIPPIN, M.D.

ASSOCIATE IN MEDICINE

PHILADELPHIA, PA.

(From the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania and the Medical Clinic, Hospital of the University of Pennsylvania)

THE effect of penicillin in 71 cases of acute coccal meningitis has been studied and an evaluation attempted both in terms of gross mortality figures and in terms of clinical response in patients seen at various stages of the disease. Certain observations have been possible with regard to dosage, schedules, routes of administration and the concomitant use of sulfonamides.

Acute bacterial meningitides, produced by organisms other than the meningococcus, are always sporadic and usually occur secondarily to infection elsewhere in the body or following direct traumatic contamination. While sulfonamide therapy has been unusually successful in meningococcal meningitis and moderately so in streptococcal meningitis, it has been of limited value in the pneumococcal and staphylococcal varieties. Today, the reported death rates in meningococcal meningitis are often less than 5% and rarely exceed 10%.<sup>5</sup> The effectiveness of the sulfonamides in acute streptococcal infections and especially those in the rigid, pneumatic chambers of the head such as

\* The work described in this report was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Pennsylvania.

† Drs. White and Murphy are now serving with the armed services. Dr. Lockwood is now Associate Professor of Surgery, Yale University Medical School.



mastoiditis and sinusitis has resulted in a marked reduction in the incidence of streptococcal meningitis. Not only has the early use of sulfonamides in these localized infections prevented hazardous complications, but they have been effective in reducing the mortality in established streptococcal meningitis from more than 90% to less than 35%.<sup>2</sup>

With this decline in the incidence of streptococcal meningitis, the pneumococcal infection has become the greatest problem, from the standpoint of frequency, mortality, and relative resistance to sulfonamide treatment. Before the use of chemotherapy, only an occasional patient recovered from pneumococcal meningitis. Sulfonamide therapy has resulted in widely diverse experiences in these infections, probably because of the limited number of cases and their tremendous variation in severity and extent of involvement. Today, the overall mortality in this disease is probably in the neighborhood of 80%.<sup>5</sup>

Many reports in which sulfonamide therapy was used show a much lower death rate; however, the numerous isolated unreported fatal cases must be taken into consideration. This is supported by the report of Dowling *et al.*<sup>3</sup> who surveyed the results in Washington, D. C., from January 1, 1938, to December 31, 1941, and found that only 4 of 72 cases survived. All 72 of these patients received sulfonamide therapy and many were given specific serum in addition.

Staphylococcal meningitis is considerably more uncommon than any of the other meningitides caused by cocci. In spite of chemotherapy, the death rate in this disease has remained high, although occasional recoveries have been reported.

In view of the powerful action of penicillin against coccal infections, it was hoped that the results in meningitis caused by these organisms could be significantly improved. This report comprises the results obtained in 71 patients with acute meningitis who were treated with penicillin. These cases were distributed as follows: 50 pneumococcal, 12 meningococcal, 5 streptococcal, and 4 staphylococcal meningitis. We have attempted to evaluate the effectiveness of penicillin without the addition of other forms of therapy, although with few exceptions these patients had received sulfonamides prior to the use of penicillin and in 10 cases a combination of penicillin and sulfonamides was used.

This study was made possible by the cooperation of a large number of physicians in 18 hospitals in the Philadelphia area. Approximately 60% of the cases were treated in teaching institutions. The authors controlled the dosage in all cases and the routes and intervals of administration in most of them. We attempted to see the patients frequently or follow their course through communication with their attending physicians. The general management and supportive care was left to the discretion of the physician in attendance. We feel that this type of experience enhances the value of the results obtained, since it offers an indication as to what may be expected in purulent meningitis with the more general use of the drug; however, limitations of supply and the lack of prolonged experience with the drug probably altered the final outcome in many of the 71 cases.

**Pneumococcic Meningitis.** In this series of 50 cases of pneumococcic meningitis treated with penicillin, the mortality was 64%. In comparison with more recent reports on sulfonamide therapy, this does not suggest that any very significant advance has been made. Rhoads *et al.*<sup>12</sup> reported 22 patients treated with sulfapyridine and specific serum with a mortality of 68%. Neal and her associates<sup>8</sup> presented 30 cases with 67% mortality. More recently Hodes, Smith and Ickes<sup>6</sup> reported 60 cases with a final mortality of only 58.3%. Waring and Smith<sup>15</sup> published a series of 12 cases treated with combined penicillin and sulfonamide therapy with only 1 death. The higher mortality in our series may have been significantly influenced by the large proportion of aged patients, several of whom died of secondary non-infectious complications, and the inadequacy of therapy in many of the first cases treated, both in respect to total daily dosage and the duration of treatment. Of the patients in this series, 7 were given combined penicillin and sulfonamide therapy, 4 of whom died, giving approximately the same ratio of fatalities as in the entire group.

One of the most striking features of pneumococcal meningitis is the diversity in form of its clinical course. This is particularly obvious when these cases are compared with the more uniform meningococcal meningitis. In our experience the most important variables which influence survival, other than those pertaining to specific therapy, are age and the source of infection. The patients in this series varied from 1 month to 72 years of age; 21 were less than 16 years of age, 12 of whom (57.1%) died. Further breakdown of these 21 cases does not reveal any significant difference between infants and older children. Of 12 patients, 31 to 50 years of age, only 5 (42%) succumbed to the disease. Of 17 patients over 50 years of age, only 2 recovered (Table 1).

TABLE 1.—PNEUMOCOCCIC MENINGITIS (SIGNIFICANCE OF AGE)

Age group (yrs.)	Recovered	Died
Less than 2 . . . . .	5	7
2-5 . . . . .	2	1
6-15 . . . . .	2	4
16-30 . . . . .	0	0
31-50 . . . . .	7	5
51 and over . . . . .	2	15

Pneumococcal meningitis in 29 cases occurred secondarily to uncontrolled infection in the air-containing spaces of the head. In 23 instances the primary focus was found in the middle ear or mastoid, and in 6 in the paranasal sinuses. Of the patients, 9 developed meningitis subsequent to pneumonia, in only 5 of whom were the blood cultures positive. The primary focus was not determined in 12. The mortality in the 29 cases having foci in the head was 71.4% and 55.5% in the 9 cases occurring secondarily to pneumonia. In those with undetermined foci, 6 (50%) died. Many of these foci were not determined until necropsy was performed. The higher death rate in those having subcranial foci indicates the inadequacy of penicillin alone in effectively controlling these infections (Table 2).



from 7 of the meningitic infections, 4 of which resulted from otitic foci. This agrees with the findings of other investigators.<sup>2,3</sup> Types III, IV and V produced approximately one-third of the infections, while Types I through VIII were the responsible organisms in 26 of the 46 pneumococcus typed cases. The primary infection in 17 of the 26 was otitis media or mastoiditis. Meningitis secondary to pneumococcal pneumonia and sinusitis appeared to be more random in regard to specific types. There was no essential difference in mortality between the infections produced by the lower types and the higher types of pneumococci.

Blood cultures were done in 41 of the 50 cases, 23 of whom demonstrated bacteremias while 18 did not. The mortality was somewhat greater with bacteremia. Three bacteremic cases displayed acute vegetative endocarditis at autopsy. This complication was suspected in another fatal case upon whom necropsy was not performed (Table 3).

TABLE 3.—PNEUMOCOCCIC MENINGITIS (SIGNIFICANCE OF BACTEREMIA)

	Recovered	Died	Total
With bacteremia . . . . .	8	15	23
Without bacteremia . . . . .	8	10	18
No blood culture . . . . .	2	7	9
Total . . . . .	18	32	50

The systemic dosage of penicillin varied widely. During the early part of this study supplies of the drug were usually limited and occasionally treatment had to be discontinued because of exhaustion of supply. The later patients in the series were given 100,000 units per day to adults, adjusting the route of administration, intramuscular or continuous intravenous, to the acuteness and severity of the individual case. (There is a trend toward giving larger doses of penicillin in severe infections, now justified by the increasing availability of the drug, and in view of our relatively unsatisfactory results with the dosage we have employed, it would appear to be wise to give at least 200,000 units per day during the acute phase of the disease.) The smallest daily dose used in any of these cases was 25,000 units in infants, and 50,000 units in adults. The largest dose given was 180,000 units each day to an adult whose infection was extremely acute and severe. Among patients who recovered, the average total dosage was 1,400,000 units and the average duration of treatment was 15.5 days.

Nineteen patients received intramuscular therapy in equally divided doses every 2 or 3 hours, 12 of whom recovered with a resultant mortality of 37%. The remaining 31 cases received intravenous therapy, either throughout their course of treatment or until they improved sufficiently to justify a change in administration. Twenty-five (80.6%) of these patients died. These figures do not assign any significance to the route of administration since the more acutely ill patients received intravenous therapy.

*Intrathecal Therapy.* The work of Rammelkamp and Keefer<sup>11</sup> with normal subjects indicated that intravenously administered penicillin

did not readily cross the blood-brain barrier and that intrathecal therapy was necessary for the successful treatment of meningitis. Rosenberg and Sylvester<sup>14</sup> recently reported the recovery of effective concentrations of the drug in the spinal fluid of patients with meningitis following systemic administration of 20,000 to 40,000 units. Pileher and Meacham,<sup>9</sup> studying the effect of penicillin on experimental staphylococcal brain lesions in dogs, found that the survival rate with intravenous penicillin was essentially the same as in the control cases, while intrathecal therapy resulted in a reduction in mortality from 93% in control animals to 54% in the experimental animals. All but 7 of the 50 cases in our series received intrathecal therapy. Three of the 7 recovered and 4 died. In 2 of the 3 recoveries response to systemic therapy was prompt, but the 3rd case became spastic and improved very slowly. Of the 4 who died, 2 were under treatment less than 24 hours and 2 demonstrated tremendously increased spinal fluid pressure. It would not be wise to rely upon local therapy alone in pneumococcal meningitis, since the primary foci of infection are seldom, if ever, in adequate contact with the spinal fluid. Pileher and Meacham,<sup>10</sup> working with experimental pneumococcal meningitis in dogs, not only demonstrated the advantages of intrathecal therapy, but also showed that local therapy alone was not adequate.

The intrathecal administration of penicillin can be carried out by injecting the material intraspinally, intracisternally, and intraventricularly. The latter may be accomplished through the open anterior fontanelle of infants, while the use of this route in older children and adults, of course, necessitates making burr holes in the skull. Two infants, one 4 weeks of age and the other 4 months old, received intraventricular penicillin through the anterior fontanelle. The older patient recovered, the other died within 48 hours without evidence of trauma or reaction to the procedure. Intracisternal penicillin therapy was given to 15 patients without ill-effects, except in 2 instances in which the fluid was slightly bloody at the next tap. Both of these patients recovered from their meningitis, although 1 died subsequently from other causes. In this group of cases it is impossible to compare adequately the results obtained with intracisternal or intraventricular therapy and intraspinal therapy, since the routes of administration were frequently combined, or altered as the patient's condition changed. However, the mortality in 28 who received local therapy by the lumbar route alone was 75%, while in the group of 15 cases who received some penicillin at a higher site of injection it was only 46.7%. This appears to suggest superiority of the intracisternal and intraventricular administration over the intraspinal route. Rammelkamp and Keefer<sup>11</sup> reported that the drug was detectable in the spinal fluid within the skull after intraspinal administration, but in many patients with purulent meningitis there may be a partial mechanical block from plastic exudate. Four patients who had failed to improve with intraspinal therapy responded promptly to intracisternal administration. All 4 recovered.

We have increased the range of intrathecal dosage since we treated the 1st case by this technic  $1\frac{1}{2}$  years ago. Of the 43 cases who were given this type of therapy, 21 received 10,000 units per day and one-third of them recovered. Of 14 who received smaller doses, 10 (71.4%) died. The administration of 15,000 to 20,000 units intrathecally each day to 8 patients resulted in a mortality of 50%. The drug was usually given intrathecally only once a day. Three acutely ill patients were injected twice daily. All 3 died. The smallest volume used for intrathecal injection was 3 cc. in infants and the largest 20 cc. in adults. The usual volume was 10 cc. per injection. Both physiological salt solution and spinal fluid were used as diluents.

The only significant reaction observed as a consequence of the intrathecal use of penicillin is occasional pleocytosis of the spinal fluid. This reaction is becoming more infrequent as the processes of manufacture permit the production of a more refined penicillin. Four patients in this series developed pleocytosis and all of them died while the fluid was still cloudy; however, there was no evidence of blockage or increased intracranial pressure.

*Adequacy of Therapy.* If one considers only those cases who received at least 100,000 units in the first 24 hours, supplemented with 10,000 units intrathecally and did not die of other causes, it appears that the 26 cases so qualified showed a mortality of 42.3%.

In our results there is no significant correlation between the onset of the disease and the date when penicillin treatment was instituted. Twenty cases treated within the first 44 hours of the disease showed a mortality of 70%, while 18 treated after 6 or more days showed essentially the same death ratio. Those treated between the 3rd and 5th day of the disease showed recovery of 7 out of 12 cases. This difference probably is not significant because of the small series; however, the results may have been influenced by the highly lethal fulminating cases on the one hand, and the more established lesions in those with older infections on the other.

All but 3 patients in this series had received sulfonamide therapy prior to the administration of penicillin. Sulfonamide treatment was usually discontinued when penicillin was started, although in 7 cases a combination of penicillin and sulfonamide therapy was administered when the former drug alone appeared inadequate. Three of these recovered. Specific antipneumococcic serum was used in conjunction with sulfonamide therapy and penicillin in 3 of the 47 cases, and only 1 recovered.

*Reactions.* The administration of penicillin did not appear to be harmful in 45 of the patients. As mentioned above, pleocytosis occurred in 4 individuals, while 1 patient developed a generalized urticaria. All 5 of these patients died. Whether or not these reactions played any significant part in contributing to death could not be determined. In a 9-months-old infant who displayed a pneumococcus Type XIV meningitis which arose from bilateral mastoiditis, the course of systemic and intrathecal therapy was prolonged and given in adequate concentrations by suitable techniques. This child showed

an oscillating response, for at times he seemed to improve, only to show cloudy fluid again after a few days. Every effort was made to control this infection over a period of 32 days, including the addition of sulfonamide therapy and the administration of specific sera intravenously and intrathecally. Penicillin was administered twice daily intraspinaly for 8 days. While there was never any evidence of penicillin reaction, about a week before death *B. coli* appeared in the spinal fluid. In spite of renewed efforts, the patient died and at autopsy the pneumococcus Type XIV and *B. coli* were cultured from the meninges. It was at necropsy that the bilateral mastoiditis was finally established. While this case does not illustrate a drug reaction, in fact, the child seemed to improve on penicillin, it does adequately emphasize the possibilities of contamination and the need for strictest asepsis in subarachnoid punctures.

Two patients, 1 of whom recovered, showed evidence of marked crystalluria, hematuria, and possible ureteral blockage from sulfonamide administration prior to the use of penicillin. Another patient receiving combined therapy developed a skin rash and a bilateral conjunctivitis, both of which quickly disappeared after the sulfonamide was discontinued. Penicillin was not stopped until the patient had recovered.

The development of localized or generalized spasticity and psychosis was a common occurrence in this series of cases. Four children became spastic, 3 of whom survived. In all 3 the spasticity improved slowly after the infection was controlled. One of these patients who recovered did not receive any intrathecal therapy. There were 4 patients who showed mental disturbances, only 1 of whom recovered from the infection. This patient was transferred to a mental institution soon after penicillin was discontinued where she remained for 3½ months before she died.

*Deaths.* Of the 32 deaths in this series, 12 occurred in the first 48 hours after penicillin treatment was started. The remaining 20 cases, after 2 days of therapy, showed varying degrees of response prior to death. Some of them improved only slightly, while others were apparently cured of meningeal infection and succumbed to other complications.

Necropsies were performed on 20 of the 32 fatal cases. The cause of death in 10 of the 20 was thought to be an overwhelming meningitis. The extent of involvement in these cases varied from a localized basilar meningitis to panmeningeal involvement. In 4 cases secondary brain abscesses were thought to be the principal cause of death. Positive blood cultures had been obtained in only 1 of the 4. The rupture of a lung abscess resulted in death of a 7-year-old boy, in whom the meningitis was improving on penicillin therapy. Another patient, a 66-year-old woman, died with a lung abscess and considerable cerebral deterioration several weeks after meningitis had been controlled. Three cases were found to have acute vegetative pneumococcal endocarditis at autopsy. The remaining patient had apparently recovered from his meningitis and was being treated for a concomitant

putrid empyema which ruptured into the bronchus and resulted in suffocation.

**Meningococcal Meningitis.** Meads, Harris, Samper and Finland<sup>7</sup> recently reported 9 cases of meningococcal meningitis treated with intrathecal and systemic penicillin. They studied these patients exhaustively and concluded that the response to penicillin in meningococcal meningitis is somewhat slower than to the sulfonamides. They also found that several strains of meningococci recovered from these patients were relatively resistant to penicillin. Rosenberg and Arling<sup>13</sup> reported 71 cases treated with penicillin with only 1 fatality; however, it is not known whether sulfonamides were incorporated in the treatment or not.

Our results in 12 cases, in which there were 6 deaths, are not indicative of the effectiveness of penicillin, but serve to illustrate the limitations of this drug in controlling the more severe and resistant meningococcal infections (Table 4). Seven of the 12 patients were given penicillin after adequate sulfonamide therapy had failed. In 2 of the 7 there was no bacteriologic evidence of infection when penicillin was started. Four of these 7 patients died.

TABLE 4.—MENINGOCOCCAL MENINGITIS

No.	Age	Sex	Bacteremia	Daily penicillin dosage		Results
				Systemic	Local	
1	27	M	No	100,000	None	Rec.
2	25	F	Yes	100,000	None	Rec.
3	63	M	No	100,000	10,000	Died
4	5	M	(No cult.)	50,000	None	Rec.
5	31	F	Yes	100,000	None	Died*
6	37	M	No	100,000	None	Rec.
7	2	F	Yes	50,000	None	Died
8	21	M	No	100,000	None	Died
9	2	M	No	100,000	16,800	Died
10	15	F	Yes	100,000	10,000	Rec.*
11	1	F	Yes	100,000	62,000	Rec.
12	47	F	No	100,000	10,000	Died

\* Waterhouse-Friderichsen syndrome.

The remaining 5 cases included 2 who had received less than 8 hours of sulfonamide therapy and 3 who were given penicillin as the primary and only form of therapy. Two of the 5 patients were *in extremis* and died within 24 hours after penicillin was started. One of them had been given 2 doses of sulfadiazine.

Penicillin and sulfonamides were combined in 2 patients, both of whom recovered.

The systemic dosage used was 100,000 units daily except for 2 children, both of whom received 50,000 units each day. The drug was given by continuous intravenous drip during the acute phase in 9 cases and by intramuscular injection in 3, all children. Among those who recovered, the average total dose was 750,000 units during an average of 6.5 days of treatment.

The 2 fatal cases who were *in extremis* when penicillin was started had an inadequate period of therapy in respect to duration and total



dosage. The 4 remaining cases which terminated fatally received ample therapy.

Only 5 of the 12 patients were given intrathecal therapy. Three of the 5 died. The intraspinal route was used in 3; the intraeisternal method in 2. The daily intrathecal dosage in 3 patients was 10,000 units, 16,800 units in another, and the remaining patient received 20,000, 41,000, 63,000 and 50,000 units at various times. There was no evidence of reaction to intrathecal administration in any of the 5.

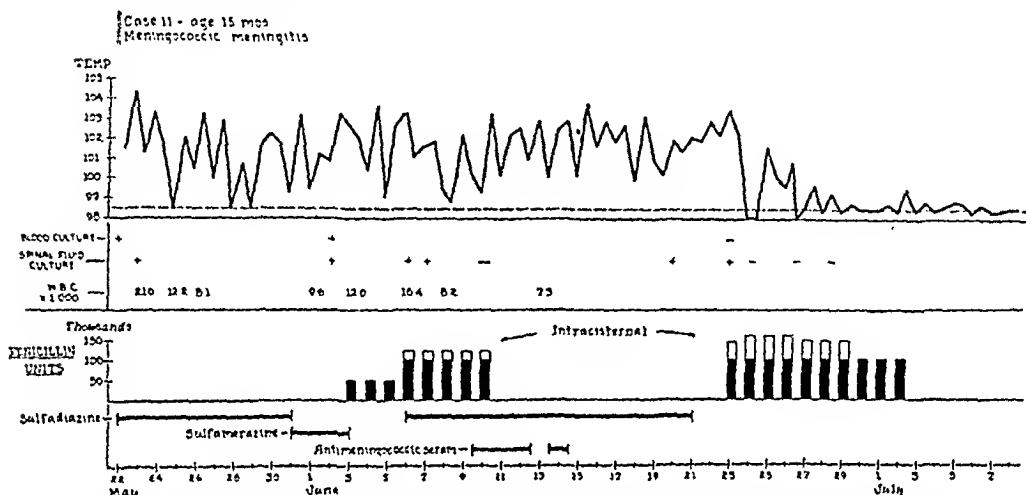


CHART 2.—Highly resistant meningococcal meningitis treated with massive intracisternal penicillin therapy (as high as 62,000 units daily) resulting in prompt response.

**Case Abstract.** The patient who received the massive intracisternal therapy (Chart 2) was a 15-month-old white female. She was admitted to the hospital on May 22, 1944, with acute meningococcemia and meningitis. Sulfonamide therapy was given in large doses until June 3, 1944, without significantly altering the course of the disease. The bacteria remained present both in the spinal fluid and blood. Sulfonamide was discontinued on June 3, 1944, and a course of penicillin therapy begun. She received 50,000 units daily by intramuscular injection without appreciable effect. On June 6, 1944, the systemic dosage was increased to 100,000 units daily. In addition, 20,000 units were given intracisternally and sulfadiazine was again added to the treatment. By June 10, 1944, there was still no therapeutic response and penicillin was discontinued. A combination of massive sulfonamide therapy and intermittent specific serum injections were continued until June 21, 1944. All forms of therapy were then stopped for 54 hours, during which time the temperature rose slightly and the child became much more toxic. On June 23, 1944, the blood culture was sterile, but the spinal fluid still contained viable meningococci. On this date systemic penicillin therapy of approximately 100,000 units each day was started again. Sulfonamides were not given. Along with the systemic penicillin, the following doses were given intracisternally: June 23, 41,000 units; June 24, 62,000 units; June 25, 62,000 units; June 26, 62,000 units; and 50,000 units June 27, 28 and 29. With this massive therapy the child began to improve promptly, the spinal fluid became sterile and began to clear and by June 28 the temperature approached the normal range and did not exceed 99.6° F. thereafter. She was discharged from the hospital July 11, 1944, completely cured.

Seven patients received no intrathecal therapy, 3 of whom were given no sulfonamide medication. There were 3 deaths among the

7 cases, 1 occurring in a patient who received only penicillin. The recovery of 4 patients with systemic therapy alone, all of whom had positive spinal fluid cultures when penicillin was started, suggested that systemically administered penicillin does cross the blood-brain barrier in sufficient concentration to be effective in some cases.

Among the 6 patients who recovered, 3 responded promptly in a manner similar to the usual sulfonamide effect (Chart 3). The remaining 3 showed varying degrees of delay in response. All 3 had received sulfonamide therapy previously and it was combined with penicillin in 2 of the 3 cases. This experience does not indicate any significant lag in response to penicillin as compared with the sulfonamides.

Case 6 - age 37  
Meningococcal Meningitis

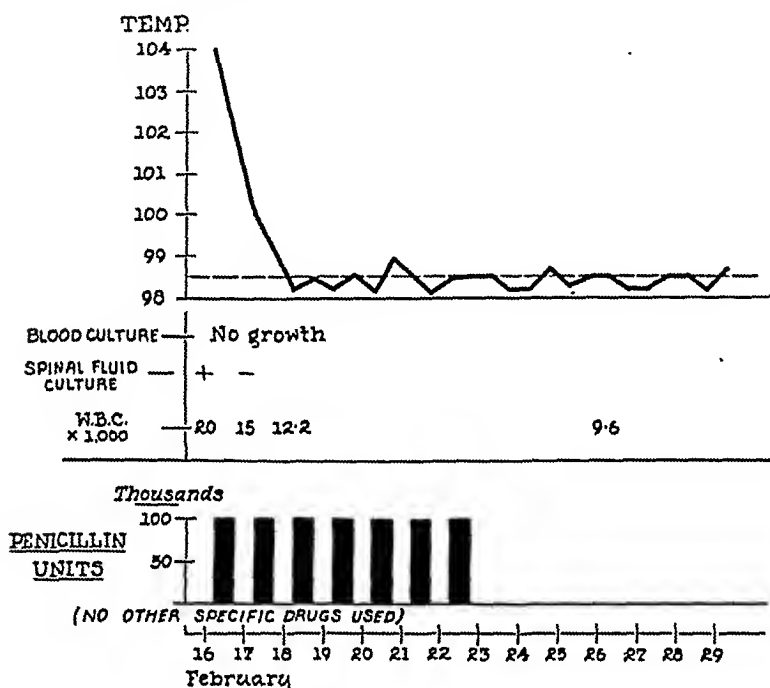


CHART 3.—Meningococcal meningitis showing prompt response to systemic penicillin therapy alone.

Two of the 12 patients demonstrated findings suggestive of a Waterhouse-Friderichsen syndrome. One patient who died 12 hours after the onset of the disease was found to have a hemorrhagic right adrenal at necropsy. She had meningococcemia as well as meningitis. The other patient, a girl of 15, had an acute onset associated with nausea, vomiting and abdominal pain and distention. A rash appeared approximately 12 hours later and the patient was semicomatose and in shock soon thereafter. The rash which at first was petechial and distributed chiefly to the extremities and face, soon became dark and blotchy. At the time of admission the temperature was over 107° F.

The blood pressure was consistently low for 5 days after admission to the hospital and the blotchy purpuric areas progressed to gangrene and sloughing which greatly delayed her final recovery. Penicillin was started soon after admission and was given intrathecally as well as intravenously. Two days after admission sulfadiazine was added to the therapy, since she had remained unconscious and febrile. She responded very slowly but with progressive gradual improvement.

**Streptococcal Meningitis.** Our experience with penicillin therapy in acute streptococcal meningitis has not been significant because of the limited number of cases and their extreme complexity. These results are included merely for the sake of completeness and to demonstrate the limitations of penicillin therapy, even in infections caused by highly susceptible organisms, when there is a preponderance of circumstances which limit or prevent the possibilities of recovery. Only patients who had failed to respond to sulfonamide treatment were given penicillin.

Five patients with streptococcal meningitis were treated with penicillin and only 1 of the 5 recovered (Table 5). Three of the 4 fatalities occurred in patients who were moribund at the onset of penicillin therapy, 2 of whom died within 36 hours. The single recovery occurred in an infant 3 months of age in whom meningitis developed secondary to a bilateral otitis media. Penicillin was started soon after admission before the child had received any other form of therapy. For 2 days she received 100,000 units daily by equal 2-hourly intramuscular injections. Thereafter for 4 days she was given 50,000 units each day by the same route. Ten thousand units were given intracisternally each day in conjunction with the systemic therapy. Systemic sulfadiazine was started on the 4th day of penicillin treatment since the fluid was still cloudy, although sterile culture was obtained; the temperature had remained elevated and nuchal rigidity was still present. Sulfadiazine was continued for 12 days after penicillin had been discontinued. Bilateral myringotomy was done soon after admission. In this case it is impossible to determine the respective rôles which penicillin, sulfadiazine and myringotomy played in contributing to recovery.

TABLE 5.—STREPTOCOCCAL MENINGITIS

No.	Age	Sex	Bacteremia	Daily penicillin dosage		Results
				Systemic	Local	
1 . . . . .	10	M	No	80,000	10,000	Died
2 . . . . .	76	M	Yes	100,000	10,000	Died
3 . . . . .	52	M	Yes	150,000	10,000	Died
4 . . . . .	60	F	No	90,000	10,000	Died
5 . . . . .	3/12	F	(No cult.)	100,000	10,000	Rec.

Among the 4 patients who died, 1 was 10 years of age, while the others were 52, 60 and 76 years old respectively. All 4 had received an ample course of sulfonamides prior to the use of penicillin. The drugs were not given together in any of the 5. All 4 received adequate intravenous and intrathecal penicillin therapy. There were no sulfonamide or penicillin reactions of any kind. One of the 4 received

3 intraventricular instillations of the drug before she died, 36 hours after penicillin was started. In 3 of the 4 the spinal fluid had become sterile before penicillin was started. In the remaining case only 1 fluid specimen was obtained, since the patient died within 24 hours.

The primary foci of infection among the fatal cases were found to be: otitis media, cellulitis of the eye with osteomyelitis of the orbit, an infected cerebellar scar (which was incised), and a diabetic foot infection which resulted in bacteremia and endocarditis as well as meningitis.

The organism in 4 of the 5 cases was beta-hemolytic streptococcus, while the spinal fluid of the 5th patient revealed anaerobic non-hemolytic streptococci. The cause of death in 2 cases was listed as purulent basilar meningitis, as subdural abscess in another, and as acute endocarditis in the remaining case.

**Staphylococcal Meningitis.** The results obtained with sulfonamide therapy in staphylococcal meningitis have been less satisfactory than those obtained with sulfonamides in other forms of acute coccal meningitis. This disease is the more infrequent of the secondary meningitides and has always been considered to be more lethal.

The great specificity and potency of penicillin against hemolytic *Staphylococcus aureus* infections is well illustrated in the 4 patients included in this series (Table 6). All 4 of them recovered from their acute infection, although 1 of them died 3½ months after the infection had been controlled and apparently eliminated by the use of penicillin. This patient was a 22-year-old female, admitted because of sensory disturbances in the lower extremities. A staphylococcal bacteremia and meningitis developed subsequently which was treated successfully with penicillin. During her course of acute infection and therapy she displayed localizing signs. A laminectomy was done between D<sub>4</sub> and D<sub>6</sub> which revealed a subdural abscess and cord compression. The infection had apparently extended into the vertebra. Subsequently the patient developed a cord bladder, loss of sensory and motor power in the left lower extremity, and large decubiti over the bony prominences in the involved areas. She lived almost 4 months after the laminectomy. A septic abortion 3 months before admission may have been the original portal of entry.

TABLE 6.—STAPHYLOCOCCAL MENINGITIS

No.	Age	Focus	Bacteremia	Daily penicillin dosage		Results
				Systemic	Local	
1 . . .	33	L2	No	100,000	None	Rec.
2 . . .	3	Craniotomy	(No cult.)	50,000	10,000	Rec.
3 . . .	22	Uterus?	Yes	100,000	10,000	Rec.*
4 . . .	3	Craniotomy	No	25,000	10,000	Rec.

\* Died 2½ months after meningitis was cured.

The other 3 patients included 2 3-year-old children who developed meningitis as a postoperative complication following removal of cerebellar tumors. The remaining case (Chart 4) was an adult who displayed chronic recurrent osteomyelitis which, at this admission,

involved the second lumbar vertebra. He displayed left ear deafness, left arm paralysis, and acute staphylococcal sinusitis during the acute infection. None of these last 3 patients showed staphylococemia.

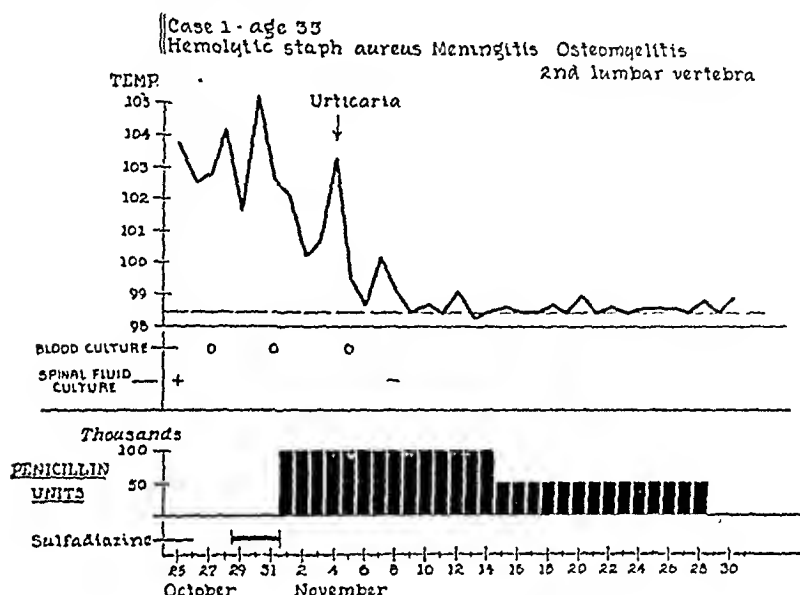


CHART 4.—Hemolytic staphylococcus meningitis treated with systemic penicillin therapy alone.

The 2 adult patients were given 100,000 units of penicillin each day, first by the continuous intravenous route and later by intermittent intramuscular injection. The 2 children received 25,000 units and 50,000 units, respectively, each day by intramuscular administration.

Intrathecal therapy in the 2 children was given intraventricularly through the operative cranial defect. The patient with the subdural abscess was given intracisternal therapy. The remaining patient who had osteomyelitis of the second lumbar vertebra did not receive any intrathecal therapy (Chart 4). His response was prompt and adequate to the systemic therapy. He displayed an urticarial rash 4 days after penicillin was started.

These patients had all received sulfonamides before the institution of penicillin treatment, but progress was not considered to be satisfactory. The evidence of meningitis in all 4 cases consisted of purulent spinal fluid containing viable organisms withdrawn on at least 2 occasions before penicillin was begun. The hemolytic *Staphylococcus aureus* was recovered in all 4.

**Discussion.** Despite the limitations of penicillin in purulent coccal meningitides, it appears that this drug will find a place in the therapy of these diseases unless it is supplanted by a more efficacious drug. While future study may reveal that the sulfonamides are equally or more effective in meningococcal and streptococcal meningitis, penicillin should be employed in those cases which do not respond after adequate trial of sulfonamides. It seems probable that penicillin will be the

primary drug of choice in the pneumococcal and staphylococcal meningitis.

There are now 2 major questions which confront us regarding the use of penicillin in meningitis. First, should it be given in combination with sulfonamides? And second, is intrathecal therapy necessary? In view of our experience and the reports which have appeared in the literature on this subject,<sup>7,9,10,13,14</sup> we believe that both questions should be answered in the affirmative.

Since penicillin and sulfonamides have been shown to be of definite value in types of meningitis discussed in this paper, and since they are, as far as we know, completely compatible, there is no rational reason for not combining them. When the 2 drugs are used simultaneously the combined result may be due to synergistic action,<sup>1</sup> or merely to the cumulative effect. Although combining of therapeutic agents may be unsatisfactory from the standpoint of clinical research, suppurative meningitis is an exceedingly serious type of infection and the combined use of all available measures of possible therapeutic value would appear to be justified in routine practice (Table 7).

TABLE 7.—COMBINED PENICILLIN AND SULFONAMIDE THERAPY

Meningitis	Recovered	Died	Total
Pneumococcal . . . . .	3	4	7
Meningococcal . . . . .	2	0	2
Streptococcal . . . . .	1	0	1
Staphylococcal . . . . .	0	0	0
Total . . . . .	6	4	10

The question of intrathecal therapy is far from settled. In this report we have mentioned 15 patients treated with penicillin alone who did not receive intrathecal injections. Eight of these patients recovered, apparently as a result of this therapy. These cases are distributed as follows: 7 pneumococcal infections with 4 deaths, 7 meningococcal with 3 deaths, and 1 staphylococcal, who survived. This indicates that intrathecal treatment is not always indispensable, but while doubt remains, we are disposed toward the opinion that the severity of these infections calls for complete therapeusis by all rational methods (Table 8). Furthermore, penicillin injected by ventricular and cisternal routes is likely to be more effective than that given into the lumbar canal.

TABLE 8.—PATIENTS RECEIVING ONLY SYSTEMIC PENICILLIN THERAPY

Meningitis	Recovered	Died	Total
Pneumococcal . . . . .	3	4	7
Meningococcal . . . . .	4	3	7
Streptococcal . . . . .	0	0	0
Staphylococcal . . . . .	1	0	1
Total . . . . .	8	7	15

The results presented in this report indicate that results with penicillin in pneumococcal meningitis are not significantly better than those obtained with sulfonamides in the hands of experienced clinicians. However, improved results with penicillin are to be expected as clinical experience increases and as cases are treated earlier in their course. The statistical results in this study were heavily weighted

by the inclusion of many patients who had already failed to respond to sulfonamide treatment. If more of the patients had received penicillin early, rather than as a measure of desperation, a larger proportion of survivals might have been recorded.

Virtually the same comments apply in connection with meningococcal meningitis.

The streptococcal meningitis patients in this series were at such advanced states of illness that there remained no reasonable expectation of successful treatment.

Penicillin appears most highly specific for the staphylococcal infections and should be used promptly as the drug of choice in all cases of meningitis caused by this organism.

Since the great majority of cases of streptococcal, pneumococcal and staphylococcal meningitis are secondary to infection elsewhere in the body, an intensive search for every possible focus is imperative.<sup>4</sup> Every patient should be examined by a competent otolaryngologist, and complete Roentgen ray studies of mastoids and paranasal sinuses should be performed with due recognition of the frequency with which the signs of infection in these areas are masked by chemotherapy. The urgency of this step is based on the likelihood that the drug therapy will not influence a primary suppurative focus and that constant refeeding of blood stream and meninges from such a focus will militate strongly against recovery. The slightest evidence of undrained abscesses in mastoids or sinuses demands early surgical intervention, even though such findings would not call for surgery in the absence of meningitis. Operative procedures are relatively safe in a patient protected against generalization of infection by penicillin.

Our random experience in the treatment of 71 cases of acute meningitis with penicillin during the period of preliminary clinical evaluation of the drug does not justify specifications of the ideal regimen of therapy in the management of these infections, particularly when the factors of increasing supply and decreasing costs of penicillin are taken into consideration. However, it appears that the following comprises a safe and useful plan of therapy until more extensive investigation establishes an optimal course of treatment:

1. Prompt diagnosis and ample supportive therapy, including surgical intervention if indicated.

2. Two hundred thousand units of penicillin administered systemically each day by the continuous intravenous route during the acute phase of the disease and later by intermittent intramuscular injection as the infection is brought under control.

3. Ten thousand to 20,000 units of penicillin intracisternally once or twice each day.

4. Ample sulfadiazine or sulfamerazine therapy systemically to attain blood levels of over 15 mg. % of free drug in conjunction with the administration of penicillin.

5. Continuation of intracisternal penicillin until 4 days after the spinal fluid has cleared and nuchal rigidity has begun to decrease, and of systemic penicillin therapy until 7 to 10 days after the disappearance of all signs of infection.

**Summary.** Seventy-one cases of acute coccal meningitis treated with penicillin are presented. The following conclusions seem justified:

1. Penicillin was often effective in pneumococcal, meningococcal and streptococcal meningitis after adequate sulfonamide therapy had failed to produce the desired response.

2. In pneumococcal meningitis the presence of subcranial foci and advanced age were cardinal factors in influencing the mortality rate.

3. Intrathecal penicillin therapy does not appear harmful. Intracisternal injection seems to be the most effective route of intrathecal administration.

4. Although penicillin administered by the systemic route alone may have a curative effect in selected cases, it seems preferable to supplement systemic administration with intrathecal injections of the drug by the cisternal route.

5. The superiority of penicillin over other forms of chemotherapy is most clearly demonstrated in staphylococcic meningitis.

6. It is not unlikely that best results will be obtained through the use of a combination of penicillin and sulfonamides in systemic therapy, and penicillin intrathecally.

7. A plan of management of purulent meningitis based upon the authors' experience, is outlined.

#### REFERENCES

1. BIGGER, J. W.: Synergic Action of Penicillin and Sulfonamides, *Lancet*, 2, 142, 1944.
2. DINGLE, J. H., and FINLAND, M.: Diagnosis, Treatment, and Prevention of Meningococcal Meningitis With a Résumé of the Practical Aspects of Treatment of Other Bacterial Meningitides, *War Med.*, 2, 1, 1942.
3. DOWLING, H. F., DAUER, C. C., FELDMAN, H. A., and HARTMAN, C. R.: Pneumococcal Meningitis: A Study of Seventy-two Cases, *New England J. Med.*, 226, 1015, 1942.
4. FLIPPIN, H. F., and LOCKWOOD, J. S.: Sulfathiazole and Sulfapyridine in the Treatment of Pneumococcal Pneumonia and Meningitis, *Med. Clin. North America*, 24, 1789, 1940.
5. FLIPPIN, H. F., REINHOLD, J. G., and GETTER, W. I.: Sulfamerazine: Clinical Evaluation in 400 Cases, *Med. Clin. North America*, p. 1447, Nov., 1943.
6. HODES, H. L., SMITH, M. H. D., and ICKES, H. J.: Sixty Cases of Pneumococcal Meningitis Treated With Sulfonamides, *J. Am. Med. Assn.*, 121, 1334, 1943.
7. MEADS, M., HARRIS, H. W., SAMPER, B. A., and FINLAND, M.: Treatment of Meningococcal Meningitis With Penicillin, *New England J. Med.*, 231, 509, 1944.
8. NEAL, J. B., APPLEBAUM, E., and JACKSON, H. W.: Sulfapyridine and Its Sodium Salt in the Treatment of Meningitis Due to the Pneumococcus and *Hæmophilus Influenzæ*, *J. Am. Med. Assn.*, 115, 2055, 1940.
9. PILCHER, C., and MEACHAM, W. F.: The Treatment of Experimental Staphylococcal Meningitis With Intrathecal Administration of Penicillin, *J. Am. Med. Assn.*, 123, 330, 1943.
10. PILCHER, C., and MEACHAM, W. F.: The Treatment of Pneumococcal Meningitis by Intrathecal Administration of Penicillin, *J. Neurosurg.*, 1, 76, 1944.
11. RAMMELKAMP, C. H., and KEEFER, C. S.: The Absorption, Excretion and Distribution of Penicillin, *J. Clin. Invest.*, 22, 425, 1943.
12. RHOADS, P. S., HOYNE, A. L., LEVIN, B., MORSEWELL, R. G., REALS, W. H., and FOX, W. W.: Treatment of Pneumococcal Meningitis, *J. Am. Med. Assn.*, 115, 917, 1940.
13. ROSENBERG, D. H., and ARLING, P. A.: Penicillin in the Treatment of Meningitis, *J. Am. Med. Assn.*, 125, 1011, 1944.
14. ROSENBERG, D. H., and SYLVESTER, J. C.: The Excretion of Penicillin in the Spinal Fluid in Meningitis, *Science*, 100, 132, 1944.
15. WARING, A. J., and SMITH, M. H. D.: Combined Penicillin and Sulfonamide Therapy in the Treatment of Pneumococcal Meningitis, *J. Am. Med. Assn.*, 126, 418, 1944.



## INFECTIVE HEPATITIS

## WITH SPECIAL REFERENCE TO PROGNOSIS

By J. BASIL RENNIE, M.D., M.R.C.P.

LECTURER IN PRACTICE OF MEDICINE, UNIVERSITY OF GLASGOW  
GLASGOW, SCOTLAND

With the technical assistance of T. G. PIRIE

(From the Gardiner Institute of Medicine, University of Glasgow, and  
The Western Infirmary)

THE epidemic prevalence of acute infective hepatitis in the past 4 years has provided evidence for prognosis. The same disease in its sporadic form (hitherto known as catarrhal jaundice) was almost always benign, but it was known that in very occasional cases the clinical picture for unknown reasons might suddenly change and fatal hepatic failure ensue. We know nothing of the frequency of this happening, since most of the cases occurred in general practice and were probably seldom published.

During the present epidemic of the disease the prognosis is obviously benign in most cases, although recovery may be delayed for 3 months. On the other hand, there is evidence that the disease may occasionally pursue a different course, and end in: (1) acute fatal necrosis; (2) sub-acute damage, going on to: (a) gradual hepatic failure, (b) cirrhosis.

A marked rise in the incidence of acute hepatic necrosis was noted by Bergstrand<sup>1</sup> during the Swedish epidemic of jaundice in 1927. In the present epidemic of infective hepatitis in England, Ford<sup>8</sup> reported 1 death from acute necrosis in 300 cases, and Lisney<sup>15</sup> considered 3 or possibly 5 individuals died of the disease out of 1062 attacked. (It is however, probable that all of these deaths were not due to *acute* necrosis.) Under exceptionally favorable circumstances, at the U. S. Army Institute of Pathology, Lucke<sup>16a</sup> was able to study 125 fatal cases occurring in an unspecified (for obvious reasons) number of cases. However, he states that "only a small fraction of the cases" end fatally. Lucke does not state how many of the deaths were due to the spontaneous disease and how many occurred after the use of yellow fever vaccine. On the other hand, Edwards<sup>6</sup> had no deaths in 64 cases and Evans<sup>7</sup> none in 65 and there were no fatalities in 170 cases reported by Cameron<sup>2</sup> in the Palestine Forces and none in 168 cases reported by Gordon<sup>9</sup> in the Middle East Forces. As fatal cases, in the Services at least, are likely to come under observation in hospitals, it seems that acute necrosis is an infrequent termination of infective hepatitis at the present time.

There is a growing amount of evidence that the liver may sustain permanent, but not immediately fatal, damage from an attack of acute infective hepatitis. Bergstrand<sup>1</sup> and Cullinan<sup>3,4</sup> described a condition of subacute necrosis of the liver characterized by prodromal symptoms like those of acute infective hepatitis, by fluctuating jaundice and by enlargement of the liver and spleen. Many of the patients died of hepatic failure after a period of months or even years; in others ascites

and a tendency to hematemesis developed; apparent recovery was noted in some, but relapse was usual. At autopsy, subacute necrosis of the liver was found. More recently, Higgins, O'Brien, Stewart and Witts<sup>12</sup> classified as subacute all cases of hepatitis in which jaundice lasted longer than 2 months and reported 7 out of 19 to be probably due to acute infective hepatitis. Of these patients, 3 died (subacute necrosis of the liver being found at autopsy), 3 recovered and 1 showed progressive hepatic disease when last seen. In 14 of Lucké's<sup>15b</sup> cases where death occurred from unrelated causes, after recovery from infective hepatitis, all the livers appeared normal grossly. In all 9 cases examined more than a month after recovery, the "parenchyma was restored completely."

The development of cirrhosis after a variable period free from symptoms was also described by Bergstrand.<sup>1</sup> Polack<sup>16</sup> reported 8 cases in young adults after an attack of acute hepatitis 3 to 8 years before. In a review of 386 cases of cirrhosis, Ratnoff and Patek<sup>19</sup> concluded that catarrhal jaundice was the probable cause in 6.5%. Rennie<sup>21</sup> observed that in 5 out of 16 patients with cirrhosis, the only known antecedent factor was an attack of "catarrhal jaundice." Some attempts have been made to detect residual hepatic damage by performing function tests on individuals who have made an apparently complete recovery from acute infective hepatitis. Soffer and Paulson<sup>22</sup> and Kornberg<sup>14</sup> found a plasma bilirubin above the accepted normal level and a diminished bilirubin clearance in reexaminations some years after the attack.

None of those patients with positive findings showed clinical evidence of hepatic disease although some complained of dyspepsia. More recently it has been reported that hippuric acid synthesis (Rennie,<sup>21</sup> Gordon<sup>9</sup>) and levulose tolerance (Rennie<sup>21</sup>) occasionally remain impaired some weeks after jaundice has disappeared. These results are inconclusive but suggest that the more modern tests of liver efficiency may reveal latent residual damage before clinical signs of cirrhosis develop.

This paper briefly summarizes the clinical manifestations shown by 39 patients in the acute stage of infective hepatitis. Six cases of subacute hepatitis and cirrhosis considered to be sequels to acute infective hepatitis are discussed in more detail. Liver efficiency tests were carried out on all patients and in many of them on numerous occasions.

In order to acquire more information about the ultimate issue of the disease it was also intended that observations should be continued after the patients were dismissed from the hospital, but present circumstances made this generally impracticable.

**Tests Used.** Hippuric acid synthesis (Quick<sup>18</sup>) as modified by Rennie,<sup>20</sup> a modified levulose tolerance test (Rennie<sup>21</sup>), estimation of plasma albumin and globulin (Howe<sup>13</sup> as modified by Hawk and Bergeim<sup>10</sup>) and the quantitative estimation of plasma bilirubin by the method of Thannhauser and Anderson<sup>23</sup> using the Lovibond comparator.

**Results in Controls.** *Hippuric Acid Synthesis.* The test was performed on 108 convalescent patients who were free of hepatic disease and were not suffering from any of the other conditions which diminish

the output of hippuric acid. All tests were done with the subjects in bed. Over a period of 4 hours after ingestion of 6 gm. of sodium benzoate, the mean excretion of benzoic acid (as hippuric acid) in the urine was 3.18 gm. The range was 2.40 to 4.51, S.D. 1.06 and S.E. 0.10 gm.

*The Modified Levulose Tolerance Test.* Reasons for regarding the levulose tolerance test as specific have been given elsewhere (Herbert<sup>11</sup>) and a really high blood glucose such as may occur in diabetes would appear to produce the only fallacy. The plasma levulose was estimated  $\frac{1}{2}$  and 1 hour after ingestion of 50 gm. of levulose and the higher figure considered to be the significant one. In 30 controls drawn from the staff and patients convalescent from disease not involving the liver the maximum value was 14 mg. per 100 ml. The mean was 10.33, S.D., 1.14 and S.E. 0.21 mg. The extreme upper limit of normal has been taken as 15 mg. per 100 ml.

*The Plasma Proteins.* Estimation of the plasma albumin and globulin as a test of liver efficiency is based on the view that the liver is responsible for their synthesis. A number of workers have reported that albumin falls and globulin increases in various diseases of the liver, and very marked changes have been noted in cirrhosis (Post and Patek<sup>17</sup>) and in subacute hepatitis (Higgins, O'Brien, Stewart and Witts<sup>12</sup>).

As controls, 50 blood donors were used, the samples being taken at the start of the bleeding and with minimal stasis. The results are given in Table 1.

TABLE 1.—PLASMA PROTEIN VALUES IN 50 CONTROLS  
(Gm. per 100 ml. of plasma)

	Albumin	Globulin
Range . . . .	4.19-5.78	1.48-3.09
Mean . . . .	4.91	2.33
S.D. . . . .	0.37	0.96
S.E. . . . .	0.05	0.07

*The Plasma Bilirubin.* The 50 blood donors also provided a series of observations on the bilirubin level in controls (Table 2).

TABLE 2.—PLASMA BILIRUBIN VALUES IN 50 CONTROLS

Plasma bilirubin mg. per 100 ml.	No. of cases
None detected . . . . .	28
0.0-0.2 . . . . .	8
0.2-0.4 . . . . .	12
0.4-0.6 . . . . .	2

INFECTIVE HEPATITIS—ACUTE STAGE. *Clinical Manifestations.* Out of 39 patients, 37 gave a history of symptoms, predominantly gastro-intestinal, before the appearance of jaundice, marked loss of appetite being a universal complaint. The duration of this pre-icteric stage varied greatly, being less than 1 week in 24 and more than 2 weeks in 3 instances. It is, however, probable that some patients failed to detect the jaundice at its onset. Two were confident that jaundice was the first sign of illness. Three patients stated that the urine

was dark on the first day of illness and 1 of these, a doctor, detected bile in his urine 3 days before the development of icterus. Neither duration nor severity of the pre-icteric phase was related to depth or duration of jaundice.

The frequency of the symptoms and signs found in the hospital is shown in Table 3:

TABLE 3.—FREQUENCY OF SIGNS AND SYMPTOMS IN 39 PATIENTS WITH ACUTE INFECTIVE HEPATITIS

Jaundice . . . . .	39	Headache . . . . .	9
Bile in urine . . . . .	39	Joint pains . . . . .	8
Marked anorexia . . . . .	39	Albuminuria . . . . .	7
Nausea . . . . .	30	Pain in back . . . . .	3
Vomiting . . . . .	25	Spleen palpable . . . . .	2
Abdominal pain or discomfort . . . . .	25	Rash . . . . .	2
Liver enlarged . . . . .	23	Hemorrhagic tendency . . . . .	2
Liver tender . . . . .	18	Ascites . . . . .	2
Pulse rate <60 p.m. . . . .	21	Edema . . . . .	1
Fever . . . . .	13	Herpes . . . . .	1
Pruritus . . . . .	9		

Leukocyte counts were made on 25 patients. The range was 2600 to 11,000 per c.mm. Nine patients had counts of less than 5000 per c.mm. Absolute lymphocytosis was found in 5 out of 10 differential counts. Extravasation of blood after venipuncture was prominent in 2 patients with deep jaundice associated with a low prothrombin index.

CASE 2 (Table 4) is of particular interest. This patient, a man of 42, underwent laparotomy because of intense and persistent jaundice associated with a mass thought to be the gall bladder. This mass was found to be a Riedel's lobe and his gall bladder, ducts and pancreas were normal. The liver was enlarged, very hard and dark green in color. Hepatic biopsy showed a picture which could be interpreted as a stage toward recovery from severe acute hepatitis. It was of interest that although the diffuse inflammatory infiltrate had gone, there was well-marked proliferation of the bile ducts. Cirrhosis was not present. Within a few weeks jaundice disappeared and the man was dismissed well. Two years later there was no sign of hepatic disease and liver efficiency tests were normal.

This clinical and biochemical recovery from a severe lesion is in accordance with the extraordinary and rapid restoration of hepatic structure noted by Dible, McMichael and Sherlock.<sup>5</sup>

At the time of dismissal from the hospital all the patients were subjectively and objectively well save for slight or minimal jaundice which was still present in the majority. The duration of the illness varied greatly and it was not possible to assess it from any of the initial clinical manifestations save one, jaundice. If jaundice was slight it did not last long. The converse did not necessarily hold good however, as deep jaundice sometimes lasted many weeks and, on the other hand, sometimes cleared rapidly.

*Biochemical Studies.* The results of tests on 39 patients with acute infective hepatitis are given in detail in Table 4. Initial observations showed that hippuric acid synthesis and levulose tolerance were impaired in 27 cases. Plasma albumin was reduced in 27, and globulin increased in 18 out of 34 cases.

TABLE 4.—HEPATIC EFFICIENCY TESTS IN 39 CASES OF ACUTE INFECTIVE HEPATITIS

Case No.	Date	Per 100 cc. of plasma				Urine benzoic a (gm. in 4 hrs.)	Duration of jaundice (wks.) on admission
		Bilirubin (mg.)	Levulose (mg.)	Alb. (gm.)	Glob. (gm.)		
1 . . .	10/ 3/41	16.2	22.2	3.83	2.57	0.86	1
	10/17/41	3.0	18.2	3.55	2.75	1.75	
	10/25/41	1.6	13.8	4.19	3.89	2.62	
2 . . .	10/ 7/41	20.0	45.4	3.44	2.72	1.06	5
	10/25/41	3.0	24.1	3.76	2.83	2.20	
	11/ 3/41	1.8	20.6	4.41	3.97	2.48	
	11/24/41	1.3	15.0	4.28	1.76	2.43	
	10/12/43	0.2	8.8	4.95	2.11	3.67	
3 . . .	11/17/41	22.0	26.3	3.44	3.07	0.89	2
	11/24/41	4.4	13.8	4.05	2.08	1.86	
	12/ 1/41	2.4	22.2	3.75	2.65	1.06	
	12/ 8/41	1.0	12.9	4.17	2.38	2.31	
4 . . .	4/ 7/42	35.0	26.6	3.11	3.00	0.44	8
	4/14/42	26.0	19.0	3.61	2.66	0.65	
	4/21/42	7.5	15.0	3.20	3.38	1.11	
	4/28/42	3.0	13.2	4.11	3.22	0.60	
	5/ 4/42	3.0	12.8	..	..	0.74	
	5/12/42	1.4	11.1	3.88	2.86	0.92	
	7/27/42	0.2	9.8	3.94	4.20	1.20	
5 . . .	7/ 1/42	15.0	30.3	2.70	3.87	0.68	4
	7/ 7/42	9.0	36.4	2.87	4.35	0.53	
	7/15/42	2.7	18.1	3.59	4.65	0.83	
	7/22/42	1.8	22.2	3.85	3.27	0.79	
	7/29/42	1.8	20.4	4.45	3.80	1.39	
	8/ 7/42	0.6	22.3	4.11	2.54	1.56	
	8/13/42	0.6	24.4	3.71	2.77	0.92	
	8/19/42	0.4	17.1	4.38	3.18	1.72	
	8/26/42	0.5	19.0	3.88	3.65	1.84	
	9/28/42	0.2	12.5	3.82	2.97	2.01	
6 . . .	7/10/42	20.0	25.6	3.90	2.92	0.16	2
	7/15/42	20.0	35.1	3.19	3.20	0.28	
	7/22/42	18.0	34.4	3.85	3.14	0.64	
	7/29/42	18.0	36.6	4.11	3.34	0.84	
	8/ 7/42	10.0	26.6	4.89	2.73	0.98	
	8/13/42	3.0	24.4	4.39	2.58	0.92	
	8/19/42	2.6	19.3	5.30	2.93	1.45	
	8/28/42	1.8	19.2	4.63	4.05	1.72	
	10/19/43	1.3	14.2	..	..	2.26	
	4/24/44	0.4	20.3	4.62	2.57	1.80	
7 . . .	1/27/43	10.0	17.1	4.01	2.97	1.66	4
	2/ 4/43	5.5	13.0	3.88	3.04	2.62	
	2/10/43	3.5	12.5	4.19	3.17	2.66	
	10/19/43	0.6	7.8	..	..	4.44	
8 . . .	5/29/43	16.5	23.5	..	..	2.52	1
	6/ 2/43	18.0	20.8	..	..	1.66	
	6/ 4/43	22.0	23.5	..	..	1.38	
	6/10/43	22.0	26.3	..	..	0.48	
	6/14/43	21.0	30.7	..	..	1.31	
	6/21/43	16.0	23.2	..	..	1.33	
	6/28/43	6.0	24.7	..	..	1.77	
	7/ 3/43	5.3	23.8	..	..	..	
9 . . .	6/28/43	16.0	15.0	..	..	0.70	1
	7/ 3/43	15.0	29.8	..	..	0.67	
	7/10/43	3.5	26.3	..	..	1.54	
	10/26/43	0.2	23.2	5.04	2.02	3.36	

TABLE 4.—(Continued.)

Case No.	Date	Per 100 cc. of plasma				Urine benzoic acid (gm. in 4 hrs.)	Duration of jaundice (wks.) on admission
		Bilirubin (mg.)	Levulose (mg.)	Alb. (gm.)	Glob. (gm.)		
10 . . .	7/ 9/43	20.0	28.9	..	..	1.18	2
	7/13/43	28.0	31.7	3.71	3.52	1.16	
	7/20/43	18.0	24.1	..	..	1.46	
	7/28/43	7.0	18.0	..	..	2.29	
	8/27/43	0.2	13.6	..	..	2.61	
	10/24/43	0.3	14.7	5.11	2.91	3.04	
11 . . .	5/14/43	16.0	28.5	3.59	2.84	1.09	1
	5/17/43	13.0	16.4	..	..	2.05	
	5/21/43	8.0	17.2	..	..	2.14	
12 . . .	7/13/43	10.0	9.1	..	..	3.59	1
	7/18/43	7.0	..	..	..	2.76	
	7/21/43	3.0	10.2	..	..	3.57	
13 . . .	2/18/43	15.0	29.0	4.07	3.45	0.72	10
	11/ 2/43	0.2	13.1	4.88	3.37	3.51	
14 . . .	9/15/42	16.0	25.0	3.66	3.81	0.47	3
	9/22/42	12.5	26.3	4.56	3.19	0.69	
	9/29/42	6.5	14.9	4.81	3.63	1.20	
	10/ 6/42	4.5	12.5	4.52	2.70	2.38	
15 . . .	5/ 6/43	15.0	19.5	3.63	3.39	1.98	1
	5/12/43	15.0	24.3	3.62	3.19	2.05	
	5/20/43	5.0	15.2	..	..	1.10	
	5/27/43	3.2	13.8	..	..	3.18	
	10/28/43	0.3	10.2	4.50	2.75	3.18	
16 . . .	7/16/43	14.0	26.6	4.09	4.05	0.75	1
	7/21/43	10.0	24.1	..	..	1.76	
	7/27/43	4.0	15.5	..	..	2.04	
17 . . .	11/17/43	12.0	20.8	2.85	3.91	0.86	1
	11/24/43	12.0	22.7	3.41	4.96	1.34	
	12/ 7/43	5.0	13.2	4.45	5.79	3.71	
	12/24/43	..	..	..	..	3.71	
18 . . .	8/11/43	15.0	20.8	4.09	3.56	0.77	3
	8/18/43	8.0	17.4	..	..	1.83	
	8/25/43	3.6	12.5	..	..	1.83	
19 . . .	8/ 4/43	17.0	29.4	3.84	3.72	0.75	1
	8/16/43	10.0	18.2	..	..	1.12	
	8/24/43	4.5	13.3	..	..	1.92	
20 . . .	4/ 3/42	8.8	14.3	3.59	2.74	1.16	8
	4/16/42	..	14.8	4.63	2.83	2.06	
	4/24/42	3.0	9.5	3.94	2.74	2.82	
21 . . .	12/18/42	7.0	19.0	4.23	3.40	1.57	2
	12/28/42	1.2	13.9	4.11	4.69	1.35	
	10/16/43	0.2	10.6	..	..	3.01	
22 . . .	5/14/43	8.0	19.2	3.75	3.18	2.23	1
	5/17/43	3.0	14.0	..	..	2.47	
	5/21/43	0.2	12.9	..	..	3.71	
23 . . .	12/ 1/41	9.0	20.0	3.76	3.75	2.46	1
	12/17/41	0.7	7.1	5.24	1.90	2.22	
	12/10/43	0.2	8.3	5.06	2.52	2.91	
24 . . .	5/29/43	9.0	16.5	..	..	2.52	1
	6/ 2/43	4.0	10.0	..	..	2.27	
	6/ 4/43	..	..	..	..	2.79	
	6/12/43	..	..	..	..	2.82	

TABLE 4.—(Continued.)

Case No.	Date	Per 100 cc. of plasma				Urine benzoic acid (gm. in 4 hrs.)	Duration of jaundice (wks.) on admission
		Bilirubin (mg.)	Levulose (mg.)	Alb. (mg.)	Glob. (mg.)		
25 . . .	6/ 2/41	6.0	14.5	3.88	2.46	1.34	1
	11/ 9/43	0.2	15.4	4.51	3.01	3.41	
26 . . .	6/26/41	2.0	12.6	3.75	3.79	2.03	5
27 . . .	6/17/41	2.0	9.3	3.58	4.15	1.52	6
28 . . .	8/31/42	3.8	8.4	3.75	3.06	1.69	1
29 . . .	12/10/42	1.7	15.4	3.49	3.83	2.79	1
30 . . .	12/16/42	1.0	16.6	4.23	3.14	3.66	2
31 . . .	5/28/42	6.0	9.3	3.79	3.60	3.12	1
32 . . .	12/7/42	0.7	11.5	4.49	2.91	3.19	1
	11/23/43	0.2	9.7	5.13	2.68	3.06	
33 . . .	12/22/41	2.0	12.3	5.29	2.92	2.47	2
34 . . .	2/21/42	5.8	10.9	3.34	3.09	2.58	1
35 . . .	2/ 4/43	3.5	11.8	4.65	1.99	2.96	1
36 . . .	9/21/43	7.2	16.2	4.67	2.66	2.42	1
37 . . .	10/12/43	4.5	18.0	3.93	3.23	2.62	2
	12/16/43	0.3	11.2	4.54	2.53	2.53	
38 . . .	9/13/43	3.3	9.0	4.29	2.58	2.12	1
	12/19/42	0.3	10.8	4.28	2.98	3.08	
39 . . .	5/24/43	3.0	15.9	..	..	1.28	1

When plasma bilirubin was greater than 10 mg. per 100 ml., hippuric acid synthesis and levulose tolerance were invariably impaired and plasma albumin invariably below normal. Beyond this no clear-cut quantitative relationship could be made out between any of these tests performed on admission and the degree of liver damage as shown by the duration of the illness. Repeated tests, however, on 23 of the more severe cases showed clearly that the functions tested very often had not returned to normal at the time of dismissal (Table 5). In 10 patients, jaundice had disappeared and in 13 was minimal or slight, but the plasma bilirubin was still above normal in 20.

TABLE 5.—RESULTS OF TESTS AT THE TIME OF DISMISSAL (23 PATIENTS)

	No. of cases
Hippuric acid synthesis impaired . . . . .	13
Levulose tolerance impaired . . . . .	7
Plasma bilirubin > 0.6 mg. per 100 ml. . . . .	20
Plasma bilirubin > 2 mg. per 100 ml. . . . .	13

Plasma albumin and globulin, estimated in 13 patients on dismissal, were abnormal in 6 and 7 respectively.

An attempt was made to reexamine all the patients and repeat the tests, but for several reasons the results have been unsatisfactory. Of the 39 patients, 15 were in the Forces and have been lost sight of: some have been directed to work elsewhere and travel difficulties have

made others unwilling to come for examination. Data from 15 patients only have been obtained. On dismissal from hospital all but 1 of these (Case 10) showed slight jaundice and abnormality of one or more hepatic function tests. When examined 4 weeks to 29 months later, all the patients said they felt well and none showed jaundice or other evidence of hepatic disease. Hippuric acid synthesis, levulose tolerance, plasma proteins and bilirubin were within normal limits in 9 cases (Cases 2, 7, 10, 15, 21, 23, 32, 37 and 38, Table 4), but one or more tests were abnormal in 6 patients (Cases 4, 5, 6, 9, 13 and 25, Table 6).

TABLE 6.—IMPAIRMENT OF HEPATIC EFFICIENCY PERSISTING AFTER DISMISSAL FROM HOSPITAL

Case No.	Per 100 ml. of plasma				Urine benzoic a (gm. in 4 hrs.)	Time since dismissal from hospital (mos.)
	Bilirubin (mg.)	Levulose (mg.)	Alb. (gm.)	Glob. (gm.)		
4 . . . . .	0.2	9.8	3.94	4.20	1.20	2½
5* . . . . .	0.2	12.5	3.82	2.97	2.01	1
6 . . . . .	1.3	14.2	..	..	2.26	14
6 . . . . .	0.4	20.8	4.62	2.57	1.80	20
9 . . . . .	0.2	23.2	5.04	2.02	3.36	3
13 . . . . .	0.2	13.1	4.88	3.37	3.51	9
25 . . . . .	0.2	15.4	4.51	3.01	3.41	29

\* Now in A.T.S.; well; time since dismissal from hospital, 14 months.

The period of observation was short (Cases 4, 5 and 9) or the abnormalities were slight (Cases 13 and 25), but in Case 6 there was well-marked impairment of both levulose tolerance and hippuric acid synthesis in a patient without jaundice, 20 months after the attack of acute infective hepatitis.

**INFECTIVE HEPATITIS—SUBACUTE AND CHRONIC STAGE.** While clinical manifestations of subacute hepatitis or cirrhosis (chronic hepatitis) have not so far been observed in the 39 acute cases described, during the past 18 months 4 patients have been seen with striking hepatic lesions believed to be sequels to acute infective hepatitis (Cases 40 to 43, Table 7). Specimens for histologic examination were obtained either at operation or postmortem examination, and liver efficiency tests showed marked impairment of function in all the cases (Table 7).

**Case Reports.** **CASE 40.** A woman of 56 who in October 1943 developed marked anorexia and nausea. About 4 weeks later her friends remarked she was jaundiced. Jaundice became rapidly worse and persisted, although the patient thought it fluctuated in intensity. On admission to hospital in December 1943 jaundice was marked and on deep inspiration a firm smooth swelling was palpable under the right costal margin towards the midline. At laparotomy the pancreas and ducts were normal and the mass was the deeply pigmented liver. Biopsy showed great disorganization of the liver with no sign of resolution. When she was discharged from hospital, Jan. 23, 1944, jaundice was much less but the liver was still palpable and there was slight edema of the ankles. On February 16 she was readmitted because of sudden intense dyspnea and cyanosis. Her condition had deteriorated, the liver was larger, the spleen was palpable and there was ascites and considerable edema. The dyspnea was due to a very large right-sided pleural effusion. After paracentesis and salt and fluid restriction she improved and was dismissed from hospital on March 25. She died at home of hematemesis on April 20. No autopsy was made.



CASE 41. A soldier 21 years old who developed jaundice after some days of anorexia and vomiting. Numerous cases of jaundice were occurring at this time in his unit. On 2 occasions when jaundice had almost gone a relapse occurred. When admitted to hospital on Aug. 16, 1941, he had been jaundiced for 8 months. Liver dullness was diminished. The spleen was not palpable. Subsequently he was transferred to a military hospital where a laparotomy was performed. The pancreas and ducts were normal and the liver was the seat of cirrhosis. Biopsy of the liver confirmed this diagnosis. He was discharged from the Army in "fair" condition and his further history is unknown.

CASE 42. A healthy woman of 24 who in February 1939 developed anorexia, nausea, vomiting and pain in the epigastrium. Within a few days deep jaundice appeared. When this had lasted 5 months a laparotomy was performed. The bile ducts and pancreas were normal. The liver was slightly enlarged, firm and deeply pigmented. Biopsy showed healing hepatitis and early cirrhosis. The jaundice is said to have gradually disappeared and she was well save for "dyspepsia" until January 1941 when she had a slight hematemesis. In May 1941 pain in the epigastrium recurred followed by jaundice and swelling of the abdomen. On admission to this unit on June 13, 1941, there was marked jaundice and ascites. The liver was much enlarged and the spleen moderately so. Hematemesis recurred on several occasions and she died on July 12. Postmortem examination showed cirrhosis of the liver. Esophageal varices were present. Histologic examination of the liver showed well-established multilobular cirrhosis.

CASE 43. A healthy woman who in August 1942 developed jaundice after some days of epigastric discomfort, nausea and loss of appetite. When seen in hospital in November 1942 jaundice was still present, though less marked, and the liver was palpable. At laparotomy both liver and spleen were slightly enlarged. The bile ducts and pancreas were normal. Hepatic biopsy showed a mild degree of cirrhosis. When next seen in May 1943 the liver was now larger and veins were prominent on the abdominal wall. Hematemesis occurred on 2 occasions. She was re-admitted in July 1943 with severe hematemesis, from which she died. At autopsy cirrhosis of the liver with esophageal varices was found. Terminal miliary tuberculosis with infiltration of the stomach and esophagus complicated the picture. Two other patients (Cases 44 and 45) are also believed to have sustained persisting hepatic damage from an attack of acute infective hepatitis. Their illnesses also dated from a severe attack of jaundice and 1 of them has shown slight jaundice for 2 years since. Histologic confirmation of a hepatic lesion was not obtained, but both patients showed marked hepatic dysfunction.

CASE 44. A healthy man of 38 who in December 1941 developed nausea and flatulence which were followed in a few days by jaundice which was intense for 20 weeks. After this it persisted in very slight degree and he suffered from flatulent dyspepsia. In April 1943, after an attack of epigastric pain, jaundice became more marked and the stools pale for 3 weeks. Since that time there was slight jaundice, which, on admission to hospital in March 1944, was minimal. The liver and spleen were not enlarged. Blood picture and erythrocyte fragility were normal. Barium meal and enema were normal.

CASE 45. A healthy woman who in 1939 had a severe attack of jaundice lasting 4 months and during which ascites was said to have been present. Since that time there has been no jaundice and her only complaint was of being easily tired. In April 1943 she began to vomit after meals and was drowsy and irritable. On admission to hospital on April 17, 1943, there was no jaundice. Liver and spleen were not palpable. Barium meal and barium enema were negative. She improved rapidly and was dismissed symptom-free in 2 weeks.

The results of the liver efficiency tests are shown in Table 7. Plasma bilirubin was above normal in all cases but bore no relation to the severity of the condition, in Case 40 for example, falling as the patient's

condition steadily deteriorated. Levulose tolerance, hippuric acid synthesis and plasma albumin and globulin were abnormal in all the cases.

TABLE 7.—LIVER FUNCTION TESTS IN SUBACUTE HEPATITIS AND CIRRHOSIS DEVELOPING AFTER AN ATTACK OF ACUTE INFECTIVE HEPATITIS

Case No.	Date	Per 100 ml. of plasma				Urine benzoic a (gm. in 4 hrs.)
		Bilirubin (mg.)	Levulose (mg.)	Alb. (gm.)	Glob. (gm.)	
40 . . .	1/12/44	15.0	28.1	2.79	4.91	0.63
	2/17/44	5.0	43.4	2.66	5.08	0.55
	3/24/44	1.3	40.0	3.25	4.01	0.53
41 . . .	6/28/41	12.0	34.0	2.62	6.22	0.61
42 . . .	6/25/41	12.0	16.1	2.92	3.67	1.58
43 . . .	12/16/42	5.0	26.3	2.98	3.56	1.53
	1/ 7/43	8.0	32.5	3.11	4.41	1.50
	2/ 4/43	8.0	50.0	2.97	4.19	1.10
	2/11/43	4.0	41.6	2.84	3.56	1.00
	3/11/43	5.0	40.0	2.50	4.46	1.10
	5/24/43	7.0	30.7	..	..	0.69
44 . . .	3/ 3/44	2.0	36.3	3.83	4.90	1.91
45 . . .	4/13/43	0.8	26.0	..	..	1.36

**Discussion.** The number of cases studied in the early acute stage is too small to draw conclusions regarding the value of any clinical manifestation in assessment of prognosis, particularly as none of the patients died. It can be said, however, that jaundice which at its height was intense often lasted many weeks, but jaundice which was slight or moderate cleared up in 2 or 3 weeks.

The liver efficiency tests showed that even comparatively moderate attacks of acute infective hepatitis generally produced an initial impairment of all the hepatic functions investigated. One major objection commonly raised against the use of hepatic efficiency tests is that they are unlikely to be positive unless death is imminent from cholemia, so great is the hepatic reserve. Surely there is enough evidence from recently developed tests to refute this once and for all. It is also apparent that the functional impairment sometimes persisted after jaundice had gone or was minimal and even when the plasma bilirubin was within normal limits. One patient with a plasma bilirubin of 0.4 mg. per 100 ml., although clinically normal and feeling well, still showed definite impairment of hippuric acid synthesis and levulose tolerance 20 months after dismissal. Even from this single case it is justifiable to conclude that a latent chronic hepatitis can occur after an attack of acute infective hepatitis.

Further evidence of residual hepatic damage after an attack of acute infective hepatitis is afforded by 6 cases which were admitted to the wards during the 2 years of this investigation. In each case the illness started with intense, prolonged jaundice for which no known hepatotoxic agent was found responsible. One soldier patient developed jaundice during an epidemic in his unit. The existence of subacute or chronic hepatitis was confirmed by histologic examination of

4 patients, from specimens obtained at operation or autopsy. The hepatic functions investigated were grossly impaired in all. The rate of progress of the lesion varied considerably, 1 patient dying in 5 months from the onset of the jaundice and 2 others in 2 years, hematemesis being the direct cause of death. Two patients, 1 of whom still shows minimal jaundice, are leading active lives and show no gross evidence of hepatic disease, although tests show that hepatic dysfunction persists. The sixth patient has been lost sight of.

Space forbids a discussion on the relationship of the condition of the liver to the plasma proteins. A fall in albumin and a rise in globulin were encountered frequently, but since changes of the order noted in cases of acute infective hepatitis occur in many non-hepatic conditions, the test cannot be considered a specific one. More marked changes in both fractions were observed in 6 out of the 7 patients with persistent hepatic damage.

The result of this small investigation gives no answer to the question whether persisting hepatic damage is frequent after an attack of acute infective hepatitis, but gives further indication that it does occur. From the 7 examples recorded here it would seem that the condition may be clinically obvious or latent, for a time at least, and detectable only by hepatic function tests. With the records available of those who have had the disease while serving in the Forces, it should not be difficult to reach a definite conclusion by a "follow up" on a large scale.

**Summary.** 1. The occurrence and detection of residual damage to the liver after an attack of acute infective hepatitis is discussed.

2. The clinical manifestations shown by 39 patients with acute infective hepatitis are described. None died and all left hospital well or with slight jaundice only. There was a direct relationship between the depth of the jaundice and its duration, inconstant insofar as deep jaundice occasionally cleared rapidly. A biopsy was made on 1 case.

3. Hippuric acid synthesis, levulose tolerance and the estimation of plasma albumin, globulin and bilirubin were used as tests for liver damage.

4. Hippuric acid synthesis and levulose tolerance were impaired and plasma albumin invariably reduced when the plasma bilirubin was greater than 10 mg. per 100 ml., less constantly with a slighter degree of bilirubinemia.

5. Tests repeated at the time of dismissal showed that one or more functions were still abnormal in a large proportion of 23 patients.

6. Six out of 15 patients reexamined 4 weeks to 29 months after dismissal still showed abnormality of one or more hepatic function, although all felt well and showed no clinical evidence of hepatic disease. Plasma bilirubin was within normal limits in all cases. One patient showed well-marked impairment of levulose tolerance and hippuric acid synthesis 20 months after the acute attack.

7. The history, physical signs and results of liver function tests are discussed in 6 patients with hepatic disease believed to be a sequel to acute infective hepatitis. Autopsy or biopsy was made in 4 and confirmed the existence of subacute hepatitis or cirrhosis.

For the interpretation of the histology in Cases 2, 40, 42 and 43, I am indebted to Dr. Alan C. Lendrum of the Department of Pathology, University of Glasgow. My thanks are also due to Prof. J. W. McNee for his criticisms and advice.

## REFERENCES

1. BERGSTRAND, H.: Acta med. Scandinav., Suppl. 34, 1930.
2. CAMERON, J. D. S.: Quart. J. Med., 36, 139, 1943.
3. CULLINAN, E. R.: St. Bartholomew's Hosp. Rep., 49, 55, 1936.
4. CULLINAN, E. R.: Proc. Roy. Soc. Med., 32, 933, 1939.
5. DIBLE, J. H., McMICHAEL, J., and SHERLOCK, S. P. V.: Lancet, 2, 402, 1943.
6. EDWARDS, L. R. L.: Brit. Med. J., 1, 474, 1943.
7. EVANS, P.: Brit. Med. J., 2, 446, 1942.
8. FORD, J. C.: Lancet, 1, 675, 1943.
9. GORDON, I.: Brit. Med. J., 2, 807, 1943.
10. HAWK, P. B., and BERGEIM, O.: Practical Physiological Chemistry, London, Churchill, 1938.
11. HERBERT, F. K.: Biochem. J., 32, 875, 1938.
12. HIGGINS, G., O'BRIEN, J. R. P., STEWART, A., and WITTS, L. J.: Brit. Med. J., 1, 211, 1944.
13. HOWE, P. E.: J. Biol. Chem., 49, 109, 1921.
14. KORNBERG, A.: J. Clin. Invest., 21, 298, 1942.
15. LISNEY, A. A.: Proc. Roy. Soc. Med., 37, 165, 1944.
- 15a. LUCKE, B.: Am. J. Path., 20, 471, 1944.
- 15b. LUCKE, B.: Am. J. Path., 20, 595, 1944.
16. POLACK, E.: Acta med Scandinav., 93, 614, 1937.
17. POST, J., and PATEK, A. J.: Arch. Int. Med., 69, 67, 1942.
18. QUICK, A. J.: Arch. Int. Med., 57, 544, 1936.
19. RATNOFF, O. D., and PATEK, A. J.: Medicine, 21, 207, 1943.
20. RENNIE, J. B.: Brit. J. Exp. Path., 23, 329, 1942.
21. RENNIE, J. B.: Brit. J. Exp. Path., 24, 26, 1943.
22. SOFFER, L. J., and PAULSON, N.: Arch. Int. Med., 53, 809, 1934.
23. THANNHAUSER, J. E., and ANDERSON, E.: Deutsch. Arch. f. klin. Med., 137, 179, 1921.

## ORAL ADMINISTRATION TO VOLUNTEERS OF FECES FROM PATIENTS WITH HOMOLOGOUS SERUM HEPATITIS AND INFECTIOUS (EPIDEMIC) HEPATITIS\*

BY CAPT. JOHN R. NEEFE, M.C., A.U.S.

JOSEPH STOKES, JR., M.D.

AND

JOHN G. REINHOLD, PH.D.

PHILADELPHIA, PA.

(From the School of Medicine and Hospital of the University of Pennsylvania)

TRANSMISSION experiments in human volunteers<sup>1,2</sup> have shown that the causative agent of *infectious (epidemic) hepatitis* may be present in the feces of persons with the active disease. It has seemed desirable, therefore, to determine if the causative agent of *homologous serum hepatitis* is present in the feces of persons with this disease. In the present report of transmission experiments in human volunteers, the effects of the oral administration of feces obtained from patients with homologous serum hepatitis are compared with those obtained by

\* This investigation was conducted under the Commission on Measles and Mumps, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, U. S. Army, Washington, D. C.

administration of feces from patients with infectious (epidemic) hepatitis. The results of a preliminary study on the length of time the agent of infectious hepatitis persists in feces also are presented.

**Materials and Methods. Source of Material.** Feces specimens used in the investigation were obtained from two sources: (1) From volunteers with hepatitis induced by experimental inoculation with an icterogenic mumps convalescent plasma.<sup>3</sup> (2) (a) From patients with hepatitis contracted during a spontaneously occurring epidemic of infectious hepatitis;<sup>4</sup> (b) from volunteers who developed hepatitis following experimental ingestion of feces obtained from the patients mentioned under (a). All specimens were frozen within 24 to 48 hours after collection and stored at  $-5$  to  $-20^{\circ}$  C.

**Preparation of Specimens for Inoculations.** The specimens to be pooled were partially thawed and portions of each were placed in a common receptacle. The mixture was subjected to the action of a Waring Blender or an electric stirrer, distilled water being added in amount sufficient to give a fluid suspension. The homogenous suspension was then strained through 2 to 4 layers of gauze. The resulting preparations represented 10 to 50% suspensions of feces in distilled water, the concentration depending upon the water content of the original specimens. The preparations were kept at  $-5$  to  $-20^{\circ}$  C. until used in the experiments to be described. Bacteriologic examination of the individual specimens and of the final pooled preparations revealed no pathogenic bacteria.

**HOMOLOGOUS SERUM HEPATITIS FECES SPECIMENS.** The following 3 pools were prepared from specimens obtained from volunteers in various stages of the disease:

1. *Pool 1 FSH.* This was composed of portions of all feces specimens obtained from volunteer B. C. during the first 5 days after the appearance of jaundice.

2. *Pool 2 FSH.* This was composed of: (a) Pool 1 FSH plus equal volumes of (b) a pool of all specimens obtained from volunteer C. L. during the first 10 days after the appearance of jaundice plus (c) a pool of all specimens obtained from volunteer F. S. during the 7 day period immediately preceding visible jaundice and during the first 5 days after the appearance of jaundice. The final pool (2FSH) thus included portions of all specimens obtained from 1 volunteer during the pre-icteric stage and from 3 volunteers during the early icteric stage.

3. *Pool 3 FSH.* This was prepared by pooling portions of specimens obtained from: (a) Volunteer D. C., 4, 8 and 18 days after the appearance of jaundice, (b) volunteer C. E., 5 and 9 days after the appearance of jaundice, and (c) volunteer C. K., 2 and 5 days after the appearance of jaundice.

**INFECTIOUS (EPIDEMIC) HEPATITIS FECES SPECIMENS.** The following 3 pools were prepared from specimens obtained from patients in various stages of this disease:

1. *Pool 1 FIH.\** This was prepared by pooling portions of specimens obtained from: (a) Patient R. G. on the 1st day that jaundice was visible, (b) patient M. Z., 3 days after jaundice had appeared, (c) patient R. G., 9 days after the onset of infectious hepatitis without jaundice, and (d) patient H. G., 12 days after the onset of infectious hepatitis without jaundice.

2. *Pool 2 FIH.* This was prepared by pooling all feces specimens obtained from 2 volunteers (W. M., R. R. M.) during the pre-icteric, early icteric and mid-icteric stages of the disease resulting from the experimental ingestion of Pool 1 FIH.

3. *Pool 3 FIH.* This was prepared by pooling portions of the specimens obtained from the same 2 volunteers (W. M., R. R. M.) 3 weeks after disappearance of jaundice.

**Method and Route of Inoculation.** All of the pooled feces preparations were either diluted with milk (or chocolate milk) and then ingested or were injected

\* A Seitz filtrate of this pool injected into mice, guinea pigs, and monkeys, showed evidence of no other agent pathogenic for man.

into the stomach through a gastric tube. No adverse effects were noted during the immediate post-inoculation period.

*Laboratory Studies on Volunteers.* Liver function and certain other studies, using methods previously described,<sup>3</sup> were carried out at frequent intervals before and after the ingestion of the feces preparations.

**Results.** The volunteers receiving Pools 1, 2 and 3 FSH, which were prepared from feces that had been obtained from patients during the pre-icteric and icteric stages of *homologous serum hepatitis*, have been observed for 10, 7 and 4 months respectively. As shown in Table 1, none of these volunteers developed evidence of hepatitis during the period of observation. In contrast, 6 of 12 men inoculated with Pool 1 FIH, prepared from feces that had been obtained from patients with *infectious hepatitis*, contracted the disease, all within 26 days after inoculation.

TABLE 1.—RESULTS OF ORAL ADMINISTRATION OF FECES OBTAINED FROM PATIENTS WITH HOMOLOGOUS SERUM HEPATITIS AND INFECTIOUS (EPIDEMIC) HEPATITIS TO VOLUNTEERS

Feces preparation	No. inoc.	Amt. (ml.)	Route	Results			Incubation period (days)
				No. illness	Hepatitis		
					Without jaundice	With jaundice	
Pool 1 FSH*	11	4-12	I-G†	11	0	0	
Pool 2 FSH	3‡	15	I-G	3	0	0	
Pool 3 FSH	5	10	Oral	5	0	0	
Pool 1 FIH§	2	5	Oral	0	0	2	21-25
Pool 1 FIH	10	2	Oral	6	1	3	20-26
Pool 2 FIH	7	10	Oral	6	0	1	26
Pool 3 FIH	7	10	Oral	7	0	0	

\* FSH—Feces serum hepatitis.

† I-G—Intragastric, injected through gastric tube.

‡ These volunteers had received Pool 1 FSH 6 months previously. Since none of the 11 men receiving Pool 1 FSH developed hepatitis, these men were considered satisfactory for testing Pool 2 FSH.

§ FIH—Feces infectious (epidemic) hepatitis.

Pools 2 and 3 FIH were used in a preliminary attempt to determine how long the agent of infectious hepatitis continued to be excreted in the feces after recovery from the disease. One of 7 volunteers inoculated with Pool 2 FIH, representing specimens collected from the 2 patients during the active stage of the disease, developed hepatitis 26 days after inoculation. None of the 7 men inoculated with Pool 3 FIH, which was composed of specimens obtained from the same 2 patients 3 weeks after the disappearance of jaundice, developed hepatitis. Both groups have been observed for 3 months.

**Discussion.** In respect to the experiments with feces obtained from patients with homologous serum hepatitis, the pools used included many specimens from 6 different patients in various stages of the active disease. If this causative agent were commonly excreted in feces, it is probable that it would have been present in at least 1 of the 3 pools. All of the inoculated volunteers were presumably susceptible as judged by age (under 30), the absence of previous history of hepatitis, and the lack of clinical or laboratory evidence of hepatic disease. The systematic application of a group of liver function tests at least twice weekly made it improbable that a brief attack of hepatitis was overlooked. Thus, the failure of any of these men to show evidence of

hepatitis suggests that the causative agent either was not present in the feces of these patients with homologous serum hepatitis or was not active when administered by the gastro-intestinal route. This observation offers a possible explanation for one of the puzzling differences between serum and infectious (epidemic) hepatitis, namely, the apparent failure of epidemics of hepatitis to originate from patients with serum hepatitis (other than those related to the injection of homologous blood products).

**Summary.** 1. Pooled specimens of feces from 6 subjects during various stages of homologous serum hepatitis were administered orally to 19 healthy volunteers. None of these subjects showed evidence of hepatitis during a 4 to 6 month period of observation, suggesting that the causative agent either was not present in the feces or was not active when administered by the gastro-intestinal route.

2. Pooled specimens of feces from patients with infectious (epidemic) hepatitis were administered orally to healthy volunteers. Hepatitis occurred within 26 days in 6 of 12 subjects, confirming the observation of others that the causative agent is present in the feces of patients with the active disease.

3. Pooled specimens of feces obtained from 2 volunteers during the pre-icteric and icteric stages of experimentally produced infectious (epidemic) hepatitis were administered orally to 7 healthy volunteers. One developed the disease after 26 days, indicating that the agent was present in feces obtained during the active disease. Pooled specimens of feces from the same 2 volunteers 3 weeks after the disappearance of jaundice also were administered orally to 7 healthy volunteers. None developed hepatitis during a 4 month period of observation suggesting that the agent was not present in the feces 3 weeks after the disappearance of icterus.

**ACKNOWLEDGEMENT:** This investigation was made possible by the coöperation of the Administrative Staffs of Selective Service, Camp Operations Division, The National Service Board for Religious Objectors, The American Friends Service Committee, the Philadelphia State Hospital, and the New Jersey State Hospital. Invaluable assistance was rendered by Capt. S. S. Gellis, M.C., A.U.S., Dr. F. D. W. Lukens, and by the members of our laboratory staff: Mr. Charles Ming, Mrs. Mary Ming, Miss Dorothy Feinberg, Miss Arvilla Howley and Mrs. Jean Flick. We are indebted to the staff of the William Pepper Laboratory of Clinical Medicine of the University of Pennsylvania for the bacteriologic studies, to Miss Anne Messer and Miss Mary Lanning of the Biochemical Laboratory of the Philadelphia General Hospital for some of the biochemical analyses, and to the members of the laboratory staff of the New Jersey State Hospital for their wholehearted coöperation in many ways.

The authors desire to express their appreciation of the contribution made by those members of Civilian Public Service Unit No. 140 (Philadelphia, Pa.) who served as experimental subjects and to the other members of that unit, many of whom assisted materially in the conduct of this investigation.

#### REFERENCES

1. HAVENS, W. P., JR., WARD, R., DRILL, V. A., and PAUL, J. R.: Experimental Production of Hepatitis by Feeding Ictericogenic Materials, *Proc. Soc. Exp. Biol. and Med.*, 57, 206, 1944.
2. MACCALLUM, F. O., and BRADLEY, W. H.: Transmission of Infective Hepatitis to Human Volunteers, *Lancet*, 2, 228, 1944.
3. NEEFE, J. R., STOKES, J. JR., REINHOLD, J. G., and LUKENS, F. D. W.: Hepatitis Due to the Injection of Homologous Blood Products in Human Volunteers, *J. Clin. Invest.*, 23, No. 5, 836, 1944.
4. STOKES, J. JR., and NEEFE, J. R.: The Prevention and Attenuation of Infectious Hepatitis by Gamma Globulin, *J. Am. Med. Assn.*, 127, 144, 1945.

## LYMPH NODES IN LEISHMANIASIS

## REPORT ON 2 CASES

BY LT. COL. D. M. ANGEVINE, M.C., A.U.S.

CAPT. T. R. HAMILTON, M.C., A.U.S.

CAPT. F. G. WALLACE, SN.C., A.U.S.

AND

LT. COL. J. B. HAZARD, M.C., A.U.S.

FIRST MEDICAL GENERAL LABORATORY APO 519, U. S. ARMY

DESCRIPTIONS of kala azar state that the lymph nodes are frequently involved and the study of smears from excised posterior cervical or inguinal lymph nodes has been advocated as a diagnostic procedure by Cochran in 1912.<sup>1</sup> Kirk and Sati<sup>5</sup> were able to demonstrate Leishman-Donovan bodies by lymph node aspiration, in 30 consecutive cases of leishmaniasis. In a series of autopsies on 31 clinically proven cases of kala-azar, Hu<sup>4</sup> recovered parasites from the lymph nodes alone in 3 of the treated cases. No report has been found of patients with leishmaniasis presenting themselves with lymph node enlargement as the outstanding characteristic of the disease. In this connection a recent case of considerable interest is that reported by Lipscomb and Gibson<sup>6</sup> of a patient who developed visceral leishmaniasis in Malta. Tender epitrochlear cervical and inguinal lymph nodes were the only positive physical findings noted approximately 6 months before the diagnosis was established by sternal puncture, blood culture and lymph node biopsy. Smear and section of an inguinal node revealed numerous Leishmania. In reports of this disease in man little reference is made to the histopathologic picture of the lymph nodes; however, the microscopic picture in the lymph nodes of hamsters has been extensively described.<sup>2,3,7</sup>

Two soldiers recently arrived from the Mediterranean area were admitted to different U. S. Army hospitals in England, because of lymph node enlargement. No satisfactory explanation for this enlargement was found in either case, so that a cervical lymph node was removed from each patient and sent to this laboratory for histologic examination. Leishmania were demonstrated in the tissue from both, and the organism grown in culture from 1. Because of the diagnostic problem presented by the uncomplicated lymph node involvement and since we were able to obtain lymph nodes at intervals for detailed histologic study, these cases are reported.

**Case Reports.** CASE 1. A white male, air transport pilot, 22 years old, who had been in the service for 2 years, left the United States in May 1943, flew to Brazil, Dakar, and North Africa, was in Egypt for 1 week during August and in Sicily from September 1943 to January 1944. Native dogs entered the camp in Sicily. He arrived in England in February 1944, and entered a station hospital on March 7, stating that he had first noticed enlargement of the cervical lymph nodes on left side while in Sicily. Since then there had been progressive enlargement of the anterior and posterior cervical lymph



nodes bilaterally, as well as axillary, inguinal and left epitrochlear nodes. There had been no other symptoms and he felt well, having gained 5 pounds in weight during the period. He consulted a medical officer because his neck was unsightly.



FIG. 1.—Lymph node (Case 1). A, Large mononuclear cells in areas of hyperplasia ( $\times 800$ ). B, Loose spongy edematous framework in focal areas, a moderate number of lymphocytes and neutrophils are present ( $\times 440$ ). C, Parasites in lymph nodes after the second biopsy. Tissue was formalin fixed, stained with Giemsa and rapidly decolorized ( $\times 880$ ).

*Physical examination* was negative except for the lymph node enlargement. The blood count was normal, the Kahn test and Widal reaction were negative, as were the heterophil antibody and *Br. abortus* agglutination reactions. Roentgenograms of chest and neck were negative. A cervical lymph node removed on March 7 presented considerable acute inflammation with numerous Leish-

mania. The patient was transferred to a general hospital for further study on March 25. At that time the posterior cervical, auricular and suboccipital lymph nodes were bean-sized or slightly larger, discrete and not tender. The epitrochlear nodes were palpable and the inguinals not remarkable. The spleen was not felt.

*Progress Notes.* The patient was asymptomatic during his stay in hospital. The red blood count was 4,800,000, hemoglobin 96%, and white blood cells 5000 (68% neutrophils). The total serum protein was 6.5 gm. % (albumin 4.8 and globulin 1.7). A sternal puncture performed on March 27 was negative for *Leishmania*, both on smear and culture. Aspiration of a posterior auricular lymph node was negative though the material obtained appeared to be mostly blood. Three days later a second posterior cervical lymph node was removed and smear, culture on NMN (Novy-MacNeal-Nicolle) medium, and histologic sections were all positive for *Leishmania*. Two hamsters were inoculated intraperitoneally with the culture. After 1 month, 1 was killed and *Leishmania* were found in the spleen and liver.

*Treatment* consisted of 15 daily injections of 6 cc. of sodium antimony gluconate to a total of 1800 mg. At the end of the course of treatment the patient was discharged with instructions for evaluation of therapy. A third lymph node was removed from the cervical region on May 26, and no *Leishmania* were found in the histologic section.

*Pathologic Anatomy.* The first lymph node removed was enlarged, measured 1.5 x 1.7 x 1.7 cm., hemorrhagic about the periphery, rather homogenous and relatively firm. *Microscopically*, the structure of the node was partially intact and the lymph follicles somewhat indistinct, because of cellular infiltration. There was extensive hyperplasia (Fig. 1 A) and in several areas near the periphery of the node, large monocytes were arranged in clusters around pink staining material. In such areas there were considerable numbers of *Leishmania*. The parenchymal network of the node was mottled by numerous focal lighter staining, spongy, edematous and necrotic areas (Fig. 1 B). Most of the parasites were in mononuclear cells; however, in many areas the cells had apparently ruptured and organisms were extracellular. The second node presented a somewhat similar histologic picture with numerous organisms (Fig. 1 C) and several of the more cellular areas replaced by large pink staining monocytes or "epithelioid" cells arranged in focal sheets. The third lymph node was of normal size with a slightly thickened capsule, and moderate hyperplasia with an occasional giant cell. A few granular bodies, but no parasites, were observed in the sections.

CASE 2. Patient was a young adult male, admitted to hospital on Feb. 23, 1944. About 6 months previously, while in Sicily, the patient scraped the dorsum of his left hand against a wall, causing 2 abrasions. One healed promptly whereas the other became infected and did not heal for several weeks. Approximately 1 week after injury, a "sore" developed on the dorsum of the left wrist, which increased in size and resembled a carbuncle. Small amounts of pus escaped and the entire wrist was swollen, red streaks extended up the arm and tender nodules appeared in the left axilla. The abscess was incised and a considerable amount of pus evacuated. The red streaks and tender lymph nodes subsided, but the lesion did not heal and gradually ulcerated. The ulcer measured about 3.5 cm. across and healed after about 1 month. During this time, a smaller lesion that resembled a pimple developed on the left forearm. This also broke down, but healed within a short period. While in transit from North Africa in October 1943, he had a 3-day period of fever without chills. After a short time another lesion appeared on the posterior aspect of the right thigh, and a small tender rosy swelling was noted in the left groin, which gradually disappeared. Approximately 2 months before admission while shaving, the patient noticed a small lump behind the angle of the jaw on the right side. Other similar nodules appeared behind the left ear, and on the back of the neck. There had been no systemic symptoms, other than moderate anorexia and vomiting after meals on 2 occasions. The only significant findings were enlargement of

the posterior cervical lymph nodes and 1 large node at the angle of the jaw on the right. A few small firm shotty tender lymph nodes were felt in the inguinal region. The liver and spleen were not palpable. A large healed scar was present over the dorsum of the left wrist. The red blood count was



FIG. 2.—Lymph node (Case 2). *A*, Tubercle-like reaction in the perilymphatic tissues of the first lymph node removed ( $\times 100$ ). *B*, Cluster of parasites in loose stroma of the node ( $\times 2000$ ). *C*, Epithelioid cells replacing focal areas that previously contained organisms. No parasites were seen or cultured from lymph nodes with this histologic picture ( $\times 50$ ).

4,600,000, hemoglobin 90%, white blood cells 6500, with a normal differential. The Wassermann reaction and test for heterophil antibodies were negative. The patient was discharged from hospital on May 12, after receiving 6 cc. of sodium antimony gluconate twice daily for 7 days. One week after treatment, there were no palpable lymph nodes.

*Pathologic Anatomy.* A lymph node removed from back of the neck about March 7, 1944, presented a granulomatous appearance with considerable fibrosis. In the perilymphatic tissues several multinucleated giant cells were observed in circumscribed areas of inflammation, resembling tubercles (Fig. 2 A). A few questionable *Leishmania* were seen in sections stained with H & E. In Giemsa stained tissues the structure of the parasites was accentuated (Fig. 2 B) so that a diagnosis of leishmaniasis was made. A second cervical lymph node was removed in April 1944. No organisms were seen on smear, and cultures on NMN medium were negative. Approximately half of the lymphoid tissue was replaced by homogenous sheets of pink staining epithelioid cells (Fig. 2 C). No organisms were demonstrated.

**Comment.** Although it is difficult to determine the exact date of onset of the disease in these cases, it is probable that both patients contracted it in Sicily or North Africa during the latter part of 1943. Both sought medical care at approximately the same time and the initial biopsy was performed on each case in March. The second lymph nodes were removed about 1 month later and in Case 1 a third node was removed 1 month after treatment began. In Case 2 the possibility of cutaneous leishmaniasis cannot be entirely excluded; however the history strongly suggests a pyogenic infection. The anatomic location of the involved lymph nodes does not indicate any relationship with the cutaneous infection on the hand. Sternal puncture was not done to determine whether there was generalized dissemination of the organisms, because the clinical picture did not indicate visceral leishmaniasis.

*Pathologic Anatomy.* During the preparation and examination of these tissues, several points of interest became evident. On routine examination with hematoxylin and eosin stain, these bodies may be easily overlooked unless one suspects their presence. In a section through an entire node there may be no organisms, whereas in other sections from the same paraffin block, they occur in large numbers. The necessity for cutting numerous sections is obvious. The apparently larger number and size of the parasites at the periphery of the node suggests that when fixation does not reach the organisms quickly they degenerate. This indicates the advisability of bisecting the node and preparing smears before the tissue is placed in fixative. Highly satisfactory preparations were obtained with Giemsa stain on formalin fixed tissues. Differentiation was short and sections carefully decolorized in resinous alcohol. The organisms appear as dark purplish blue bodies in sharp contrast to the pale gray of the phagocytic cells. If one wishes to accentuate the organisms as an aid in their detection, this can be accomplished by quick differentiation, sacrificing, of course, the cytology of the section (Fig. 1 C).

It is not possible with only 2 cases to reconstruct accurately the pathogenesis of the disease as it occurs in lymph nodes. Nevertheless certain similar features in both cases were observed, that seem worth considering in some detail. No sections of lymph nodes were available early in the disease, and the first biopsies were obtained presumably several months after the onset. At this time there is moderate fibrosis of the capsule, and the cortical lymph sinuses are filled with mono-

nuclear cells and lymphocytes. Although the lymph follicles are discernible they are relatively indistinct and there is considerable hyperplasia in the center of the follicles as well as of the reticular network of the node (Fig. 1 *A*). Throughout the pulp there are focal areas of decreased cellularity, which represent a spongy edematous stroma (Fig. 1 *B*) in which are scattered histiocytes. Leishmania are found most frequently in such sites, both intra- and extracellularly, in somewhat greater numbers near the periphery of the lymph node. In such areas there is a tendency to form multinucleated giant cells, in which organisms are fairly numerous. In one section the capsule of the node has apparently infiltrated and a granulomatous lesion with giant cells was observed in the perilymphatic tissue (Fig. 2 *A*). From the lymph nodes removed later, it appears that the spongy focal areas which contained organisms were infiltrated with and replaced by fairly compact sheets of pink staining epithelioid cells (Fig 2 *C*). Of the 2 instances where this extensive epithelioid reaction occurred, we were unable to detect organisms either by smear, cultures or histologic sections of the nodes.

**Summary.** Two cases of leishmaniasis are described in which the primary and most important symptom was enlargement of the cervical lymph nodes. Biopsy of lymph nodes made at intervals indicate certain features that should prove helpful in establishing the diagnosis, and separating this group of cases from other chronic granulomatous lesions of lymph nodes.

#### REFERENCES

1. COCHRAN, S.: *J. Trop. Med. and Hyg.*, 16, 9, 1912.
2. HINDLE, E., and THOMPSON, J. G.: *Proc. Roy. Soc., B.*, 103, 252, 1928.
3. HU, C. H.: *Chinese Med. J.*, 47, 1112, 1933.
4. HU, C. H.: *Chinese Med. J.*, Suppl. 1, p. 1, 1936.
5. KING, R., and SATT, H. H.: *Trans. Roy. Soc. Trop. Med.*, 33, 501, 1940.
6. LIPSCOMB, F. E., and GIBSON, M. O. J.: *Brit. Med. J.*, 1, 492, 1944.
7. MELENEY, H. E.: *Am. J. Path.*, 1, 147, 1925.

---

### MITE OR SCRUB TYPHUS

#### A CLINICAL AND LABORATORY STUDY OF 64 CASES

By MAJ. THOMAS E. MACHELLA

AND

LT. COL. JAMES S. FORRESTER

U. S. ARMY MEDICAL CORPS IN INDIA

The purpose of this report is to present clinical and laboratory data on a disease encountered in this area which appears to be clinically and serologically identical with tsutsugamushi (Japanese river fever) also called mite or "scrub" typhus. Data are presented on 40 Chinese and 24 American soldiers who were admitted to this hospital during October, November and December of 1943 and January, 1944.

The presence of tsutsugamushi in Malaya was established by Dowden<sup>3</sup> in 1915. This was a typhus-like disease which differed from murine and louse-borne typhus chiefly in being transmitted by a mite

and in the Weil-Felix reaction which gave a high agglutination titer against proteus OXK and a negligible agglutination with OX2 and OX19. The clinical features of this disease included an abrupt onset, high fever, presence of a primary eschar, a maculo-papular rash occurring on the trunk, arms and legs, regional adenopathy in the area draining the site of the initial lesion, as well as generalized lymphadenopathy. The febrile illness usually lasted about 2 weeks and was followed by a lengthy convalescence marked chiefly by severe physical exhaustion. The disease was caused by a species of rickettsia. Subsequently a similar clinical picture, with the exception of the absence of a primary lesion, was described by Fletcher and Lesslar.<sup>4</sup> This was called rural typhus of Malaya and was thought to be different from tsutsugamushi because of the absence of a primary ulcer. As a result of extensive work by Lewthwaite<sup>6</sup> and his associates, it was shown that tsutsugamushi and rural typhus of Malaya were similar clinically, serologically and pathologically and that they had a common etiologic agent, namely *Rickettsia orientalis*. In this paper the disease will be referred to as mite typhus, the term "scrub" typhus being reserved for those cases of typhus-like disease in which the vector is not reasonably clear.<sup>1,5</sup> Recently, data obtained from autopsies on soldiers who served in the Buna-Gona campaign have been reported by Capt. Austin J. Corbett.<sup>2</sup>

**Procedure.** The 40 Chinese patients on whom careful and detailed clinical and laboratory observations were made, were admitted or transferred to a ward set aside for the study of this disease. Determinations of temperature, pulse and respiratory rate were made at 4-hour intervals. Daily blood pressure determinations were made. Weil-Felix reactions were run bi-weekly throughout the period of hospitalization which in most instances lasted 60 to 120 days. Determinations of blood urea nitrogen were made at bi-weekly intervals during the course of the fever. Complete blood counts (excluding erythrocytes) and urinalyses were made at weekly intervals. Each patient had a chest Roentgen ray on admission and also when a progress film was indicated. The films were interpreted by Lt. Col. P. J. Hodes. A weekly eye-ground examination was made by Capt. Harold G. Scheie. Physical examinations were made daily, concentrating especially on the appearance and distribution of rash, size of spleen and lymph nodes as well as other features pertinent to the particular case. Complete physical examinations were made and recorded every 3rd day during the early course of the disease and weekly during convalescence. Each of the Chinese had a lymph node removed for culture and microscopic study. The primary ulcer as well as portions of the skin from the site of the rash were excised in 15 cases. The results of the microscopic studies will be reported separately. In the preparation of some of the tables the duration of fever was used as the basis of comparison with other manifestations, but the duration of fever should not be considered an index of the severity of the illness. Reference to particular cases in the table will be made by numbers; Chinese 1 to 40; American 41 to 64.

**Results.** 1. INCUBATION PERIOD. The exact incubation period in the majority of instances could not be determined with certainty. The primary lesions were painless and as the troops frequently did not have an opportunity to examine their naked bodies, the time of development of the primary lesions could not be ascertained. All of the patients admitted having been in the jungle during the several weeks prior to the onset of the illness. In one American patient, in

whom the exact and only day of exposure to jungle vegetation was definitely known, the abrupt onset of his illness occurred 11 days later. The primary lesion on his arm was first noted 7 days after returning from the jungle.

TABLE 1.—LOCATION OF PRIMARY LESIONS

Site	No. of cases
Anterior neck midline . . . . .	1
Left side of neck, anterior . . . . .	2
Suprasternal notch . . . . .	1
Interascapular region . . . . .	1
Axilla (right 7, left 6) . . . . .	13
Right mammary area . . . . .	1
Costal margin, anterior (right 2, left 5) . . . . .	7
Costal margin, posterior (right 2 left 5) . . . . .	7
Antecubital space (right) . . . . .	1
Left wrist . . . . .	1
Epigastrium . . . . .	1
Left hypochondrium . . . . .	2
Inguinal (right 1, left 1) . . . . .	2
Left leg posterior . . . . .	1
Right ankle . . . . .	2

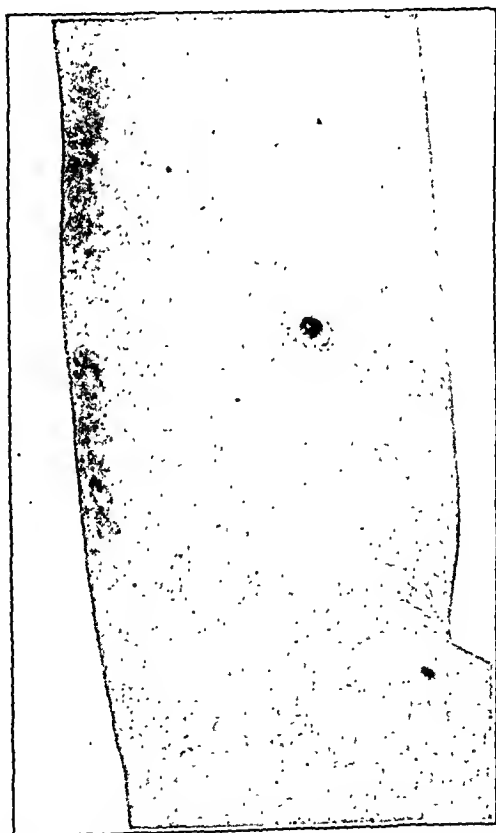


FIG. 1.—Primary ulcer on arm. Note black eschar.

2. PRIMARY ULCER. A typical primary ulcer was present in 43 out of 64 cases, an incidence of 67%. The most frequent sites of the ulcers were the upper trunk, particularly the axillæ and chest wall, anteriorly and posteriorly (Table 1). The initial lesion began as a red painless

macule which in a few days became papular. A small excoriation then appeared on the dome of the papule which soon became deeper and

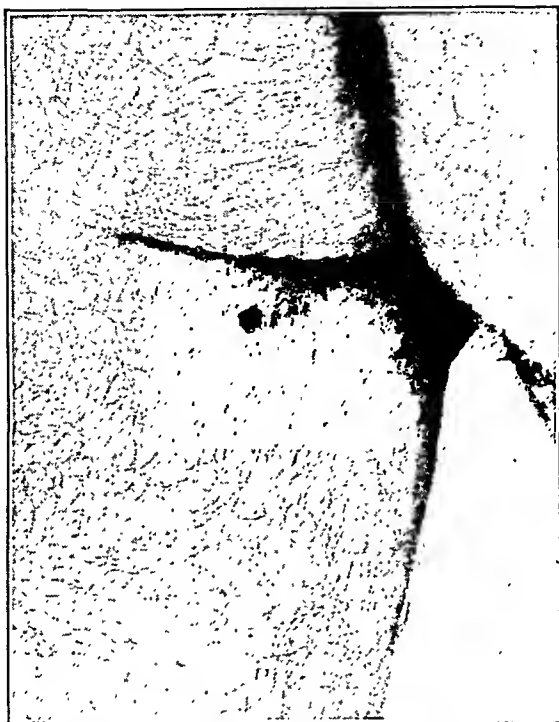


FIG. 2.—Primary ulcer on posterior aspect of left thigh.



FIG. 3.—Primary ulcer on scrotum with eschar lacking.



filled with a black eschar. (Figs. 1, 2 and 3.) Removal of the eschar left a punched-out ulcer. The typical lesion was about 5 to 7 mm. in diameter and 1 to 2 mm. deep. The average time of complete disappearance of the ulcer was on the 29th day of the disease (16 to 40 days).

3. ONSET SYMPTOMS. The onset was abrupt, with chills or chilliness, fever and headache being the most frequent symptoms. These were associated with malaise, generalized aching and marked anorexia and apathy. There was usually more than one chill, they occurred during the first 3 days and were not periodic or very severe. Cough was a prominent accompanying onset symptom in the Chinese and was frequently associated with the physical signs of bronchitis or bronchopneumonia. The head and backache were mild and in only one instance was the headache of the severity which often occurs in typhoid fever or in epidemic typhus.

Epistaxis and photophobia were occasional onset symptoms. Gastro-intestinal symptoms, aside from almost universal anorexia, were not striking; vomiting occurred in only 5 of the cases; in 3 of the Chinese, emesis ceased after roundworms were vomited. Mild diarrhea was present in 15% at the onset (Table 2).

TABLE 2.—ONSET SYMPTOMS

Symptom	Chinese, (%)	American (%)	Chinese and American (%)
Chill . . . . .	70	65	68
Fever . . . . .	94	87	90
Cough . . . . .	51	21	40
Headache . . . . .	73	82	76
Backache . . . . .	24	26	25
Vomiting . . . . .	8	8	8
Diarrhea . . . . .	10	21	15
Epistaxis . . . . .	10	4	8
Photophobia . . . . .	2	0	8
Anorexia . . . . .	93	85	88

4. GENERAL APPEARANCE OF PATIENTS. The most striking feature of the patient's general appearance was marked apathy. He felt sick and he appeared sick. He preferred to be undisturbed. He did not have the listless eye of the typhoid patient, rather the eyes were bright and alert like the "ferret-eye" of murine or epidemic typhus. This appearance differed from malaria in that the patient was sick all the time, not only during the paroxysms. His skin was often dry, ichthyotic and, in the more dehydrated cases, inelastic. He looked and felt weak, and was content to lie completely isolated from his environment and, unless urged, would disdain nourishment. Herpes simplex was noted only once.

TABLE 3.—DURATION OF FEVER IN 61 CASES

Duration of fever (days)	No. of cases		
	Chinese	American	Total
10-15 . . . . .	6	11	17
16-20 . . . . .	19	10	29
21-25 . . . . .	10	1	11
26-30 . . . . .	2	1	3
31-35 . . . . .	0	0	0
36-40 . . . . .	1	0	1

5. FEVER. The average duration of fever in 61 cases was 17.4 days, with the extremes 11 and 36 days. The average duration of fever in the Chinese patients was 18.3 days (11 to 36 days), in the Americans,

16 days (10 to 26 days); 47% of the patients had a fever which lasted 16 to 20 days (Table 3).

The type of temperature curve which the patient manifested depended on the day of the disease on which he was admitted to the hospital. The curve as seen in patients who were admitted during the first few days of the disease or in those who first developed fever while in the hospital was either typhoidal, relapsing, remittent or intermittent. During the onset of the fever the temperature would rise gradually or abruptly (Charts 1 and 2) to a level of about 103° F. and either remain elevated (Chart 3) or fluctuate in a remittent or intermittent manner (Charts 2 and 4) for the next several days. Termination of fever occurred usually by cessation of the fluctuations but in some instances, particularly in the typhoidal type of curves, the course would terminate by lysis over a period of 3 to 6 days (Chart 5). A relapsing type of fever curve was also not infrequently seen. (Charts 4 and 6.)

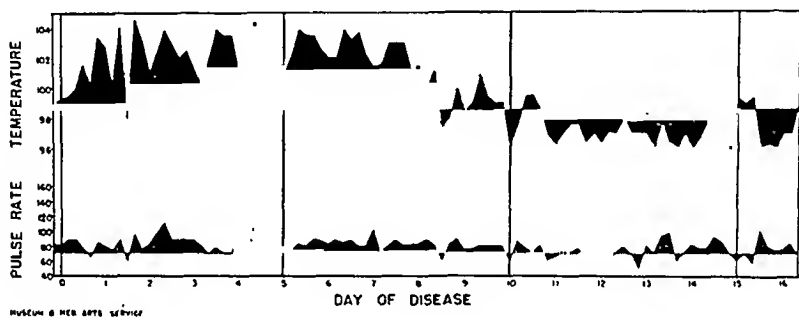


CHART 1.—Gradual onset of fever. Case 9.

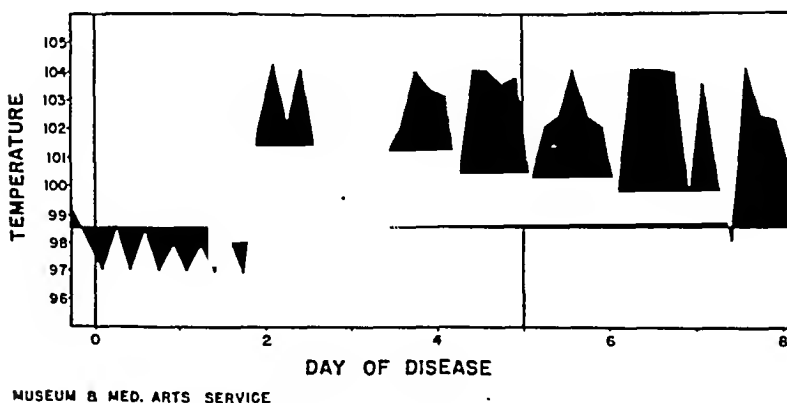


CHART 2.—Sudden onset of fever. Case 22.

The average temperature reading during the early course of the febrile period was 103° F.; on occasion, oral temperatures as high as 105° F. were recorded.

6. PULSE RATE. The average pulse rate in both the Chinese and American patients during the 1st week of the disease was elevated and averaged 102 per minute (80 to 120). This, according to Crozier-

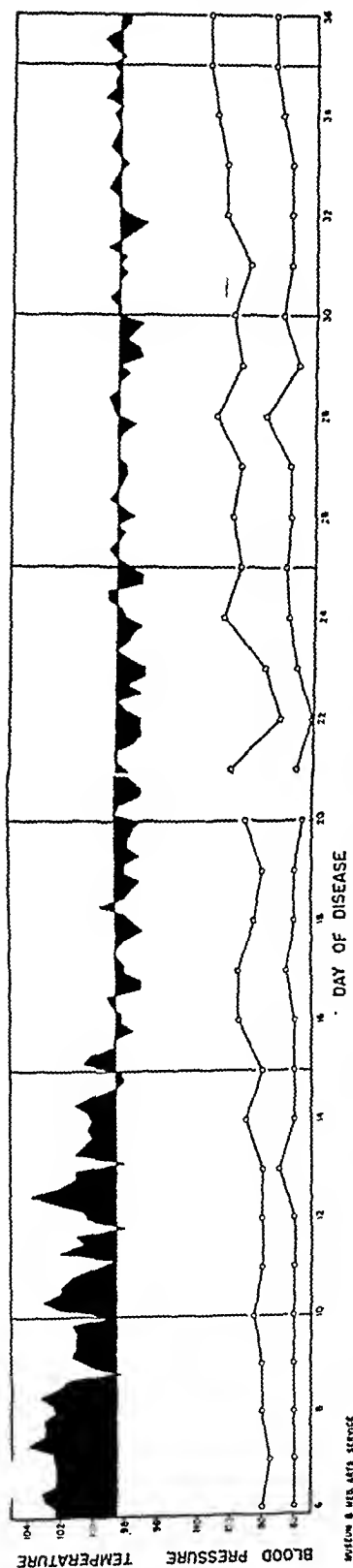


CHART 3.—Fever sustained for 4 days, then remittent for a period of 1 week. Chart also shows period of hypotension during course of fever and its disappearance during convalescence. Case 10.

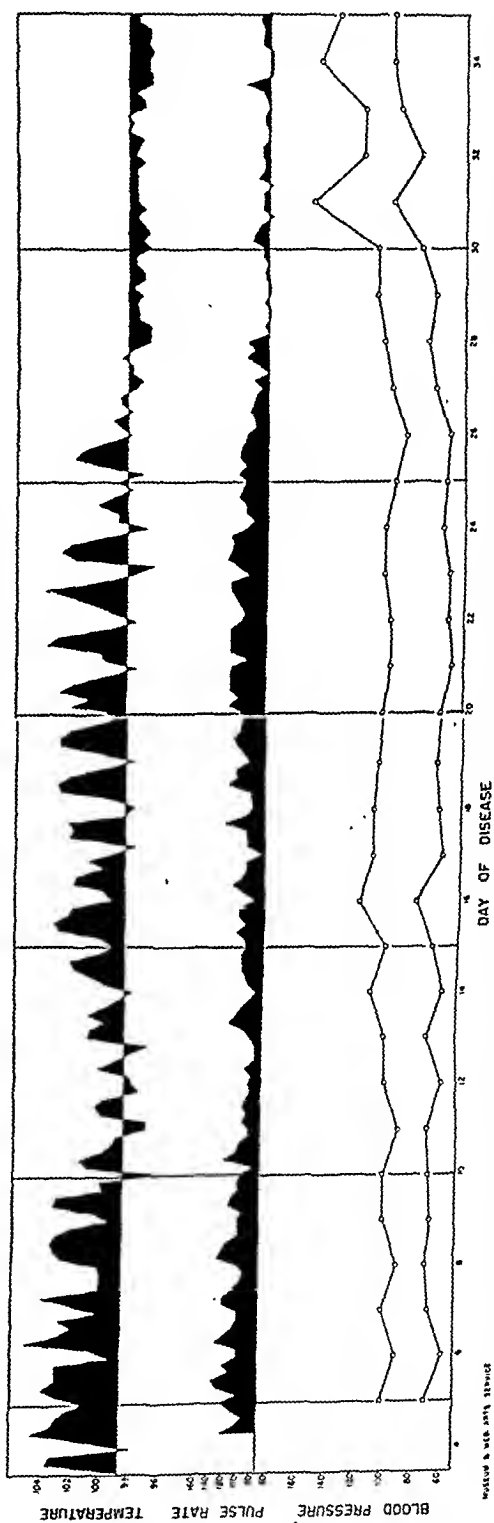


CHART 4.—Remittent type of fever curve in a patient who had a relapse of fever, a return of splenomegaly and the appearance of tender lymph nodes in the inguinal regions on the 12th day of the disease. The chart also shows hypotension during the two periods of fever with the return of blood pressure to the level presumably normal for him during convalescence. Case 12.

Griffith\* chart of temperature and pulse relationship, would indicate a relative bradycardia. During the 2nd and 3rd weeks of the disease the pulse rate was frequently more rapid, averaging 120 (110 to 140) per minute at the peaks of the temperature rises. Though no abnormalities in pulse rhythm were noted, irregularities in the pulse rate were frequent and striking. Rates varying from 110 to 140 per minute during a  $\frac{1}{2}$  hour interval were noted on numerous occasions in several patients during the latter part of the febrile period.

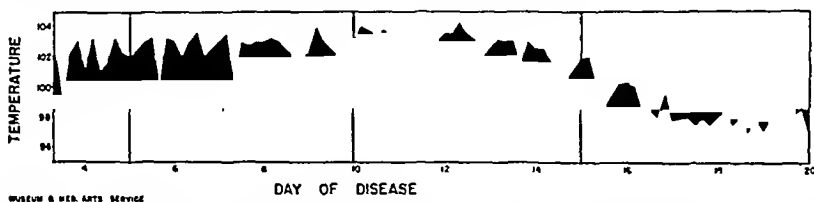


CHART 5.—Typhoidal type of fever curve with termination of fever by lysis. Case 49.

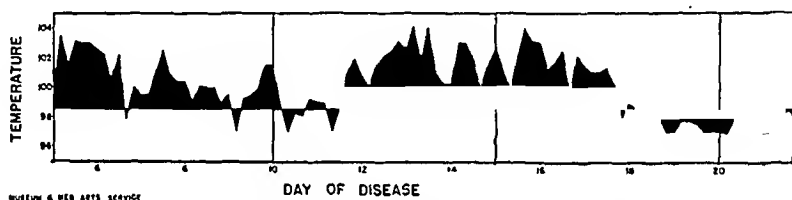


CHART 6.—Relapsing type of fever curve. Case 6.

7. BLOOD PRESSURE. In only 2 of 40 Chinese patients was the blood pressure normal from the onset of the disease throughout convalescence. In the others the blood pressure was low during the course of the febrile period and then gradually came up to normal during the period of convalescence. The fall in blood pressure applied to both systolic and diastolic levels, and when the return to normal occurred during convalescence there was no constancy in which returned first. The lowest point in the blood pressure curve was always reached at about the end of the 1st week of the disease (Charts 3 and 4). The average blood pressure reading on 35 cases early in the disease was 85/57 mm. Hg (100 to 70 systolic and 65 to 45 diastolic). When blood pressure finally returned to the level which seemed normal for the particular individual the average blood pressure reading was 120/77 (100 to 155 systolic and 70 to 100 diastolic). Return to normal occurred on the 31st day (21 to 49 days). Thus the blood pressure returned to normal after the fever subsided. Three cases of mild hypertension were observed in the series. One of these had an average blood pressure reading of 95/65 mm. Hg during the height of the disease; this gradually rose to an average of 140/95 during convalescence (Chart 4).

8. RASH AND CUTANEOUS MANIFESTATIONS. A typical rash (Fig. 4) or the remains of it was noted in 33 of 64 cases (51.5%). The inci-

\* Crozier-Griffith temperature-pulse relationships; a pulse rate of 70 per minute for a temperature of 98.3°. An increase of 10 beats per minute for each rise of 1° F. in temperature.

dence of rash among the Chinese was 50% as compared to 54.1 for the Americans. The typical rash appeared early in the course of the disease, usually between the 3rd and 6th days and lasted 3 to 5 days. In most instances the rash was maculo-papular when it first appeared, less frequently it was macular. In no instance was the rash hemorrhagic or petechial in character nor did it give rise to any subjective discomfort. As the rash subsided the residue consisted of a faint mottling which took as long as a week to disappear. In full-blown cases the rash involved the face, trunk and extremities. No case of

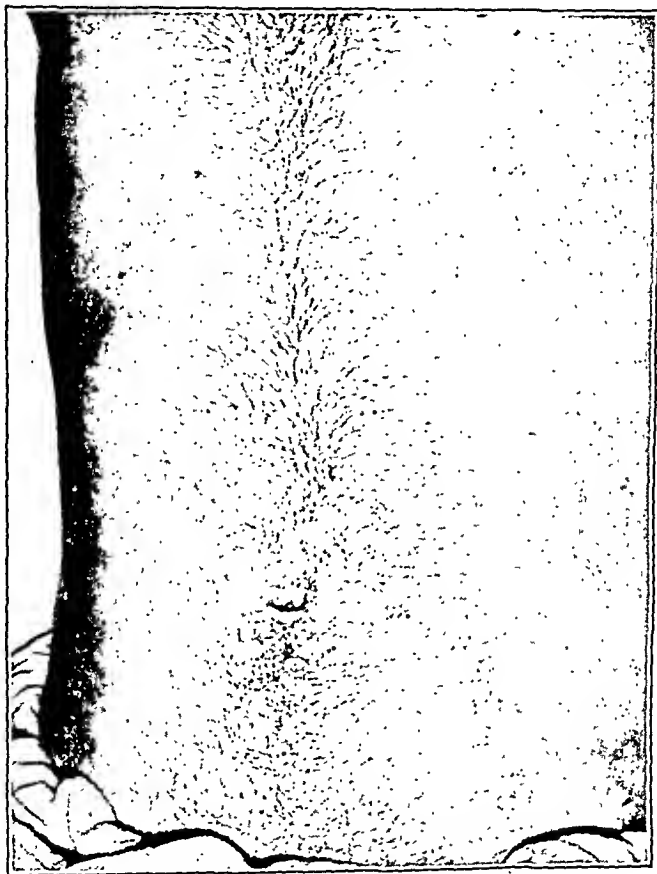


FIG. 4.—Maculo-papular rash on trunk.

involvement of the palms or soles was seen. In some cases the rash was limited to the anterior and posterior chest, abdomen and upper arms. In a few cases, only the dorsum of the chest was involved.

9. SPLENOMEGALY. The spleen was palpable during the 1st week of the disease or on admission to the hospital in 88% of 40 Chinese. In 13% of the cases with splenomegaly, tenderness of the spleen was demonstrated on palpation. This tenderness disappeared on the 10th to 14th days of the disease, even though the spleen remained palpable for a longer time. The average day of the disease on which the

spleen was no longer palpable was the 28th (12 to 53 days). In 3 instances there was a recurrence of the splenomegaly; in 1 of these, an apparent relapse of the disease occurred (Chart 4). In the other 2 cases the spleen again became palpable when a relapse of tertian malaria occurred.

10. LYMPHADENOPATHY. Regional lymphadenopathy was demonstrable in all but 4 of those patients in whom a primary eschar was present. In these exceptions the ulcer was located along the costal margins. Two Chinese patients presented enlargement and tenderness of inguinal nodes out of proportion to the enlargement of nodes elsewhere in the periphery; in neither of these cases was a primary lesion present. The inguinal adenopathy in the 2nd of these 2 cases occurred during an apparent relapse in the disease and was associated with a rise in temperature (Chart 4) and a recurrence of splenomegaly. One had to look with great care for enlargement of nodes in regions draining the site of the ulcers. In 4 instances they were found in unusual sites; the retro-sacral region, in the groove just internal to the head of the humerus, and on the lateral chest wall in the upper outer quadrant of the mammary area.

Generalized peripheral lymphadenopathy was demonstrated in 60 of 64 patients (93.7%). This lymphadenopathy developed early in the disease and was present in all cases during the 1st week of the disease at the time when regional adenopathy was also present. The general lymphadenopathy persisted for a longer time than did the regional. In 24 of the Chinese patients, no significant decrease in size of the nodes could be appreciated during the 2 to 4 months period of observation. In 16 of the cases the nodes appeared to decrease in size gradually during a period extending from the 40th to the 80th day of the disease, but in none of these did they become non-palpable.

11. CONJUNCTIVAL INJECTION. An injection of the conjunctival blood-vessels was observed, on admission, in 34 of 64 cases (53%), the incidence in both the Chinese and Americans was the same. The injection of the conjunctival vessels disappeared during the 2nd, 3rd or 4th week of the disease; most of them at the end of the 2nd or beginning of the 3rd week. In 2 of the Chinese patients, inflammation of a purulent type was present and Koch-Weeks bacilli were obtained on culture. Two others developed a corneal ulcer on the 12th day of the disease.

12. CHANGES IN THE EYE-GROUNDS. Rather characteristic changes in the eye-grounds were found in 30 of the 40 Chinese (75%) and in 14 of the 34 Americans (58%). These changes consisted of marked distention of the retinal veins, blurring of the disk margins, edema of the optic disks and retinae, hemorrhages and the development of vitreous opacities. The engorgement of the retinal veins was almost a universal finding during the end of the 1st week or the beginning of the 2nd week of the disease. The veins were markedly engorged in the extreme cases, had irregular sausage dilatation and appeared compressed at the arteriovenous crossings. Subsequently edema of the disk and surrounding retina developed in 18 of the 40 Chinese. This

edema varied in amount from less than 1 to 2 diopters. The edema was fairly diffuse usually, but occasionally was confined to the disk and was indistinguishable from a true papilledema such as is seen when intracranial pressure is increased. The cerebrospinal fluid pressure was normal in all except 1 of the patients with edema of the disks. That the swelling was not due to an optic neuritis was evidenced by the fact that visual acuity and visual fields were normal.

Four of the 18 patients who had edema of the disks developed retinal hemorrhages which were predominantly striate, but deep punctate hemorrhages were also seen along the general distribution of the veins.

"Cotton wool" exudates developed in 2 of the 18 patients who had edema of the disks. Fine vitreous opacities were seen in 7 out of the 40 patients, of which 3 had only venous engorgement as the other ocular change, while the remaining 4 had edema of the disks and retinae. The appearance of edema of disks, retinal hemorrhages, "cotton wool" exudates and vitreous opacities occurred as early as the end of the 2nd week of the disease. They persisted long into convalescence and were among the last of the abnormal findings to disappear. A detailed report of the changes in the eye-grounds will be submitted by Capt. Harold G. Seheie.

13. PULMONARY FINDINGS. Cough was a prominent symptom in 51% of the Chinese cases at the onset of the disease. Roentgen examination of the chest revealed the presence of pathologic changes in 24 of them. These consisted in the appearance of bronchitis with or without bronchopneumonia, bronchopneumonia, or enlargement of the hilar lymph nodes (Table 4). One patient had pleurisy complicating the pneumonic process. Pulmonary complications, occurring late in the disease, included pleural effusion (1 case), empyema (1 case), and lung abscess (1 case). These occurred in patients who had bronchopneumonia early in their course. The average duration of the febrile course in those patients who had acute pulmonary involvement was 2 to 4 days longer than in those who had no such complication (Table 4). One could not be certain whether the findings in the lungs which occurred early represented a complication or a part of the disease itself. The clinical and Roentgen evidence of bronchopneumonia and bronchitis disappeared during convalescence.

TABLE 4.—PULMONARY FINDINGS IN CHINESE PATIENTS PRESENT ON ADMISSION

Pulmonary lesion	No. of cases	Duration of fever (days) (average)
None	16	18
Enlargement of hilar nodes	2	18
Bronchitis	9	20
Bronchopneumonia	9	20
Bronchitis and bronchopneumonia	4	22

14. MENTAL AND NERVOUS SYSTEM MANIFESTATIONS. Symptoms referable to the mental and nervous system developed in 7 of the 40 Chinese cases and in 2 of the 24 American patients. These consisted of temporary psychosis, characterized by acute mania (1 case), disorientation and confusion (2 cases); coarse jerky movements of the eye-balls (1 case), purposeless twitchings of muscle groups of the

extremities (4 cases), paresthesias of hands and arms (1 case); generalized convulsions (2 cases); and meningismus (1 case). In all of these patients except 1, the spinal fluid cytology, serology and protein content were normal. The spinal fluid pressures were normal in all except 3 cases; in the 2 patients who had generalized convulsions they were low or zero. In the 3rd patient (Case 42) the spinal fluid pressures determined on the 14th and 17th days of the disease were elevated at 230 and 260 mm. of water and there was an increased number of cells (lymphocytes) as well as a trace of globulin present. There was no relationship between the presence or absence of azotemia and the presence of muscular twitchings, though the 2 patients who had generalized convulsions had the greatest degree of nitrogen retention. Except in 1 instance the nervous system manifestations all occurred after the 1st week of the disease, usually during the 2nd or 3rd week (Table 5). In the exception, a patient (Case 58) who developed a temporary psychosis, the mental symptoms occurred after the fever had subsided.

TABLE 5.—MENTAL AND NERVOUS SYSTEM MANIFESTATIONS

Case No.	Duration of fever (days)	Mental or nervous manifestation	Day of disease disturbance noted	Duration of disturbance (days)	Spinal fluid			Azotemia	
					Pressure in H <sub>2</sub> O	Cells	Globulin	Degree	Day of disease
36	18	Acute mania	7	1	140	0	0	0	
58	18	Disorientation, confusion, hallucinations, muscular twitching	25	25	..	..	..	0	
16	20	Twitching of muscles of hands and arms	10	3	..	..	..	0	
13	26	Coarse jerky movements of eyes	22	10	140	0	0	Plus 1	14-17
7	36	Generalized rhythmic muscular twitchings	14	11	135	0	0	Plus 1	16
3	19	Convulsion generalized; disorientation, confusion, semistupor	16	18	40	0	0	Plus 3	16-24
			19	..	0	0	0		
8	Died on 16	4 generalized convulsions, stupor	16	Died†	0	0	0	Plus 4	11-16
2	18	Paresthesias and weakness of hands and arms	14	7	..	..	..	0	
42	17	Meningismus, muscular twitchings	14	11	230 260	60 26*	Trace Trace	0	

\* 97% lymphocytes.

† Died 4 hours after first convulsion.

15. **HEPATOMEGALY.** Hepatomegaly was not a common finding in this series of patients. Significant enlargement of the liver was found only in 2 American and in 1 Chinese patient. This finding was present on admission and disappeared during convalescence.

16. **JAUNDICE.** Mild jaundice was detected in 4 of the 40 Chinese patients, not any in the Americans. This occurred late in the febrile period or early in convalescence and persisted for 9 to 22 days. The direct Van den Bergh reaction in these cases was delayed, while the indirect or quantitative reaction revealed serum bilirubin values ranging from 0.3 to 1.3 mg. per 100 cc. (Table 6.)

17. **DEAFNESS.** Deafness was complained of by 11 of the 40 Chinese patients at some time during the course of the disease. In 8 of these,



definite evidence of middle ear disease, sufficient to account for the impairment of hearing was found by Capt. Phillip A. Marden. In the remaining 3, the deafness was thought to be due to neural involvement. It was bilateral and was first complained of during the 3rd week of the disease, lasted for about 2 weeks and then disappeared. Two of these 3 patients had received quinine during the early course of the disease, hence some justifiable doubt may exist as to the exact cause of the deafness.

TABLE 6.—JAUNDICE

Case No.	Duration of fever (days)	Day of disease on which icterus was first detected	Van den Bergh reaction			Duration of icterus (days)	Anemia
			Direct reaction	Indirect in mg./100 cc. serum	Day of disease		
3	19	24	Delayed	1.3	16	18	Slight
			Delayed	0.5	33		
			Delayed	0.2	41		
7	36	19	Delayed	0.4	21	22	None
			Delayed	0.4	32		
			Delayed	0.2	41		
19	21	17	Delayed	0.4	18	10	Slight
			Delayed	0.1	27		
28	17	19	Delayed	0.3	20	18	None

18. STOMATITIS. Three of the 40 Chinese patients had a severe ulcerative stomatitis on admission, all of these were very seriously ill and 2 of them were semistuporous when admitted. One of the American patients (Case 42), who was semistuporous, developed a glossitis which disappeared during convalescence while vitamin concentrates were administered. Parotitis developed in 1 American patient (Case 49).

19. CARDIAC FINDINGS. The findings on auscultation of the heart in the 40 Chinese were not significant except for the presence of soft systolic basal murmurs, which were heard in 26 cases during the height of the illness. These disappeared during convalescence in all except 2. Electrocardiograms on 9 of the 40 patients revealed essentially normal tracings with the exception of evidence of left axis deviation in 2 (Table 7). These 2 patients also had evidence of increased heart size clinically and by Roentgen examination.

TABLE 7.—ELECTROCARDIOGRAPHIC FINDINGS

Case No.	Duration of fever (days)	Day of disease on which EKG taken	Electrocardiogram interpretation
2	18	27	Normal
3	19	10	Left axis deviation
5	24	15	Normal
7	36	15	Normal
8	Died on 16 day	11	Normal
10	16	6	Normal
12	24	4	Normal
14	14	8	Normal
33	23	20	Left axis deviation
42	17	(See Table 9)	Myocardial damage
46	10	11, 29, 43	Normal
61	13	38	Normal

In 2 of the American patients, basal systolic murmurs were heard. Another patient developed a transient pericardial friction rub on the 28th day of the disease, 19 days after fever had subsided; his blood-urea nitrogen at this time was normal though it had been elevated slightly.

during the fever. Electrocardiograms in 3 of this group of patients were made (Table 7). They were normal in 2, including the patient with the pericardial friction rub. In the 3rd patient findings suggestive of myocardial damage were obtained. This patient also had a gallop rhythm, and had evidence of partial heart block (Table 8).

TABLE 8.—ELECTROCARDIOGRAPHIC FINDINGS IN CASE 42, DURATION OF FEVER 17 DAYS

Day of disease	Rate per min.	P-R interval (sec.)	Rhythm	P waves	QRS complexes	T waves
14	150	0.16	Sinus	Inverted in L-3	Normal	Deeply notched in chest leads; rounded ST segments
17	140	0.13	Normal	Probably normal	Normal	Abnormal ST segment; flattening of T waves; notching in chest leads
29	90	0.28	Normal	Notched	Normal	Low and notched T-1 and Tcr 3, 4, 5
44	95	0.17-0.19	Normal	Inverted in L-3	Normal	Normal; T-3 inverted; slight elevation; ST segment CR-3
83	100	0.17	Normal	Normal P-3 inverted	Normal	Normal; T-3 inverted

20. RELAPSE. Although some of the patients' temperature curves were of a relapsing type, only 1 patient in the series who had such a febrile curve also developed other evidences of a relapse. He was a Chinese with no primary eschar and was admitted on the 3rd day of his disease (Case 12). His fever curve was of the remittent type (Chart 4). The temperature fluctuations became less high, and on the 12th day his temperature had become almost normal. During this time his previously enlarged spleen gradually became smaller. On the 13th day the temperature again began rising though still remittent. The spleen again became large and also tender, and huge tender lymph nodes appeared in both inguinal regions. His temperature finally became normal on the 24th day of the disease. This patient's OXK titer did not become positive until the 21st day of the disease.

21. WEIL-FELIX REACTION (OXK). In 62% of the Chinese cases the Weil-Felix reaction first became positive at the end of the 2nd week of the disease, this being the time at which the temperature became normal in the average case. In the remainder of the patients the reaction became positive either at the end of the 1st week or after the beginning of the 3rd week (Table 9).

TABLE 9.—TIME AT WHICH WEIL-FELIX REACTION BECAME POSITIVE (PROTEUS OXK)

End of week No.	No. of cases (%)
1	8.1
2	62.2
3	10.8
4	10.8
5	2.7
6	5.4

The highest titer at which agglutination occurred varied in different patients from 1/25 to 1/6400 (the most frequent titer was 1/200) (Table 10). The highest titer in most instances was obtained about 2 weeks after cessation of fever. The average day of the disease on which the titer became negative was the 68th (42nd to 122nd) in

25 cases. In 11 others the reaction was still positive at the time of discharge on the 42, 47, 49, 70, 71, 85, 92, 98 and 100th day respectively (Table 10). Variation in titer in any one patient occurred from time to time, and smooth curves were not obtained (Charts 7, 8 and 9). This was probably due to the fact that the samples of blood

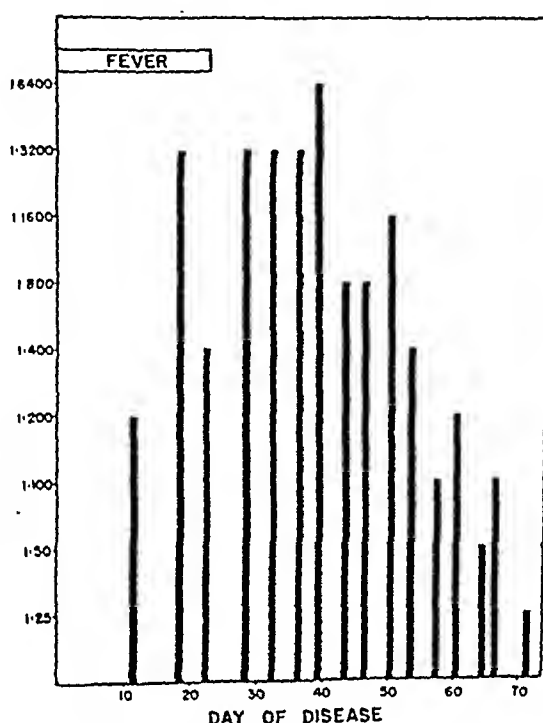
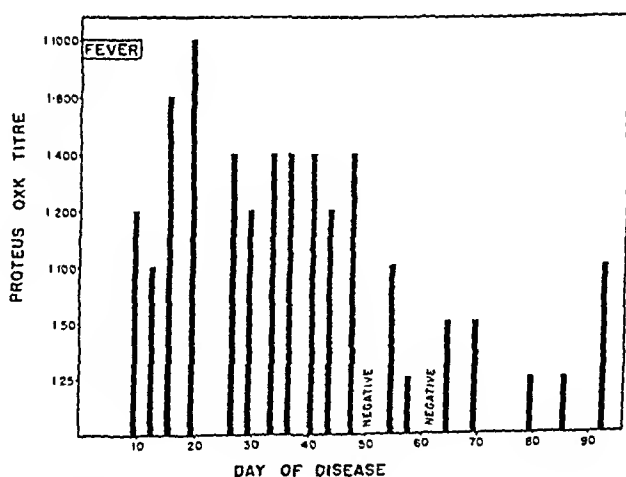


CHART 7.—High titer Weil-Felix reaction (proteus OXK) in a patient who had fever for 23 days. Case 30.



MUSEUM & MED ARTS SERVICE

CHART 8.—Moderately high titer Weil-Felix reaction (proteus OXK) in a patient who had fever for 12 days. Case 21.

on any one patient were tested on different days and with different lots of antigen.

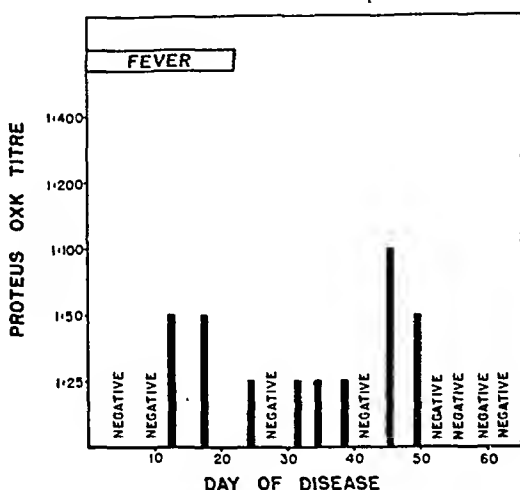


CHART 9.—Low titer Weil-Felix reaction (proteus OXK) in a patient who had fever for 22 days, a typical initial lesion, a typical rash, splenomegaly, regional and generalized lymphadenopathy and eye-ground changes. Case 31.

No significant correlation could be found between the clinical severity of the disease and the presence or absence of high titer in any single patient. The number of low, medium and high titer values was distributed about evenly in the group of patients in whom the fever lasted more than 18 days as compared to the group in which the course was shorter. However, the day of the disease on which the first positive titer was reached was on the average 7 days later in the group which had the more prolonged course of fever. The coincident existence of pneumonia did not appear to influence the titer. There was no significant difference between the length of time the titer remained positive in the group in whom the fever lasted more than 19 days as compared to the group in whom the fever lasted less (Table 10).

One factor which seemed to hold true in general was that those Chinese patients who had primary lesions had higher proteus OXK agglutination titers than the group without ulcers. In the former group, 15 of 24 patients had titers positive in a dilution greater than 1/200, while in the latter group only 1 patient had a titer in this range (Table 10).

The fact that the Americans had all been inoculated against ordinary typhus did not appear to influence either the dilution at which agglutination against proteus OXK occurred or the clinical severity of the disease.

22. PERIPHERAL BLOOD PICTURE. In the Chinese patients there was a moderate leukopenia during the 1st week of the disease, the average leukocyte count being 5500 per c.mm. in those patients who had no respiratory disease demonstrable. The mean neutrophilic percentage was 53, the lymphocytic 39, monocytic 7 and the eosinophilic 1 (Table 11). The leukopenia persisted until the end of the 4th week and then

gradually disappeared. The percentage of neutrophils gradually decreased as the lymphocytes increased, the latter reaching a maximum height at the end of the 3rd week. The percentage of monocytes remained practically at the same level throughout the period of observation. An interesting shift in the differential occurred after the 4th week of the disease (Chart 10). This was a rise in the percentage of eosinophils. The level rose from 1% during the febrile part of the disease to a level of 12 to 16 during the 6th to 12th weeks of observation. Hookworm infestation may have been responsible for the increase in total leukocyte count and the eosinophil percentage noted during convalescence. Hookworm ova were demonstrated in at least 33% of the patients.

TABLE 10.—RELATION OF PRESENCE OR ABSENCE OF PRIMARY ESCHAR TO HEIGHT OF PROTEUS OXK TITER

Case No.	Duration of fever (days)	Day of disease on which titer first became positive	Degree of positive agglutination <i>Eschar Present</i>	Day of disease titer became negative	Complication
1	24	43	1/400	85+	Bronchopneum.
2	18	15	1/200	85+	Bronchitis
8	16	0	0	..	Convul. azotemia
	(died)				
14	14	14	1/400	77	Bronchopneum.
15	24	22	1/400	63	Bronchitis
18	20	28	1/25	70	Azotemia
20	16	15	1/100	57	Azotemia
21	12	8	1/1600	92+	
22	20	15	1/1600	91	Azotemia
23	19	15	1/100		
24	19	21	1/100	64	Bronchopneum., otit. media
25	26	28	1/200	71	Bronchitis
28	17	15	1/400	64	Bronchopneum., jaundice
29	15	15	1/200	100+	Bronchopneum.
30	23	14	1/6400	71+	Bronchopneum., azotemia, anemia
31	20	14	1/100	..	Bronchopneum.
32	24	15	1/400	43	
33	23	15	1/1600	28	Azotemia
34	18	8	1/400	57	Azotemia
35	19	14	1/800	70+	Bronchitis, azotemia
36	18	14	1/200	42+	
37	16	14	1/1600	69+	Bronchopneum.
38	16	14	1/800	57+	Bronchitis, bronchopneum., azotemia
39	16	7	1/800	42	Bronchitis
40	27	22	1/1600	47+	
			<i>Eschar Absent</i>		
3	19	15	1/100	105	Azotemia
4	23	35	1/800	84	Bronchitis
5	24	29	1/200	..	Bronchopneum., pleurisy, azotemia
6	18	15	1/50	56	
7	36	35	1/200	84	Bronchopneum., azotemia
9	11	15	1/200	56	
10	16	22	1/100	63	
11	21	43	1/25	49	
12	24	21	1/200	56	Bronchopneum.
13	26	29	1/100	112	Bronchopneum., azotemia
16	20	14	1/200	85	Bronchitis
17	18	29	1/50	57	Bronchopneum.
19	21	15	1/200	92	Jaundice
26	12	15	1/200	63	Bronchopneum.
27	14	15	1/50		

The trends in the white formed elements of the peripheral blood in those patients who also had bronchopneumonia were rather similar to those described; but the initial leukopenia was slightly less (Chart 11).

A slight degree of anemia developed in the Chinese patients, the average hemoglobin decreasing from 14 to 12 gm. during the first 3 weeks of the disease. The anemia disappeared during convalescence.

TABLE 11.—FORMED ELEMENTS OF PERIPHERAL BLOOD IN UNCOMPLICATED CASES (CHINESE)

Week of disease	Average leukocyte count	Differential (%)				Hb. (gm.)	No. of Cases
		Neut.	Lymphs.	Mono.	Eosin.		
1	5500 (3400-7850)	53 (39-62)	39 (21-55)	7 (1-17)	1 (0-2)	14 (10.4-17.5)	9
2	6750 (3900-10,800)	46 (23-77)	48 (21-72)	5 (0-12)	1 (0-4)	13 (11.4-16.0)	10
3	6150 (4600-8800)	37 (11-55)	55 (42-85)	6 (2-12)	2 (0-6)	12 (9.4-13.8)	12
4	6330 (3300-8400)	44 (30-58)	48 (39-65)	6 (0-21)	2 (0-6)	13 (10.4-14.5)	12
5	7626 (3700-17,200)	44 (26-61)	40 (31-53)	8 (0-16)	8 (0-29)	12 (9.5-14.2)	12
6	7725 (4200-14,400)	46 (33-58)	33 (24-45)	5 (0-10)	16 (2-36)	12 (10.4-15.2)	11
7	8372 (4400-13,600)	39 (32-49)	40 (28-52)	8 (1-12)	13 (2-26)	13 (7.6-14.4)	11
8	9441 (5500-15,400)	40 (23-53)	38 (23-48)	6 (2-15)	16 (1-34)	12 (10.2-13.9)	12
9	9350 (6300-12,400)	44 (22-54)	38 (25-56)	6 (2-9)	12 (5-17)	13 (10.6-14.0)	11
10	8506 (3450-13,200)	44 (21-58)	35 (30-43)	6 (2-9)	15 (3-42)	14 (11.0-15.0)	8
11	8521 (6150-10,850)	47 (27-60)	34 (24-44)	5 (1-10)	14 (1-43)	13 (11.0-14.0)	7
12	8125 (6700-12,450)	48 (34-64)	35 (20-56)	5 (2-8)	12 (1-28)	13 (11.4-14.2)	6

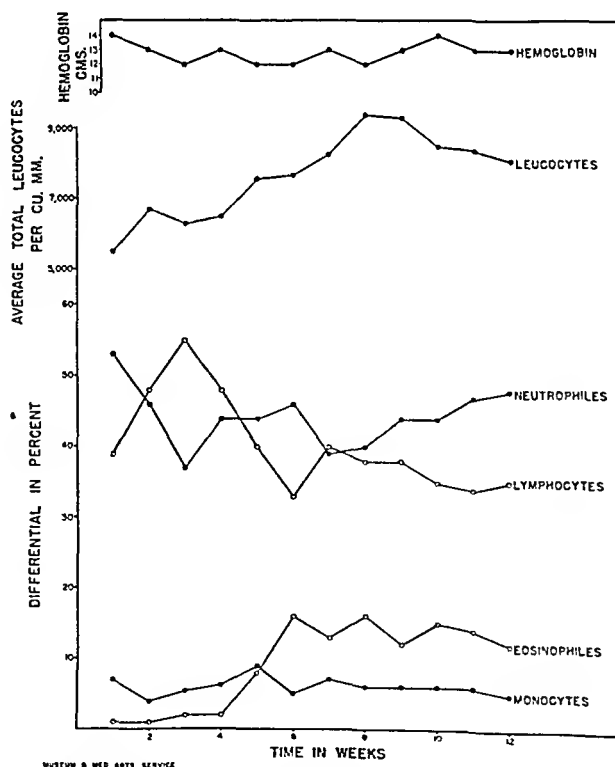


CHART 10.—Trends in the average total leukocyte count, differential and hemoglobin in Chinese patients having no evidence of pulmonary involvement. Note eosinophilia late in convalescence.

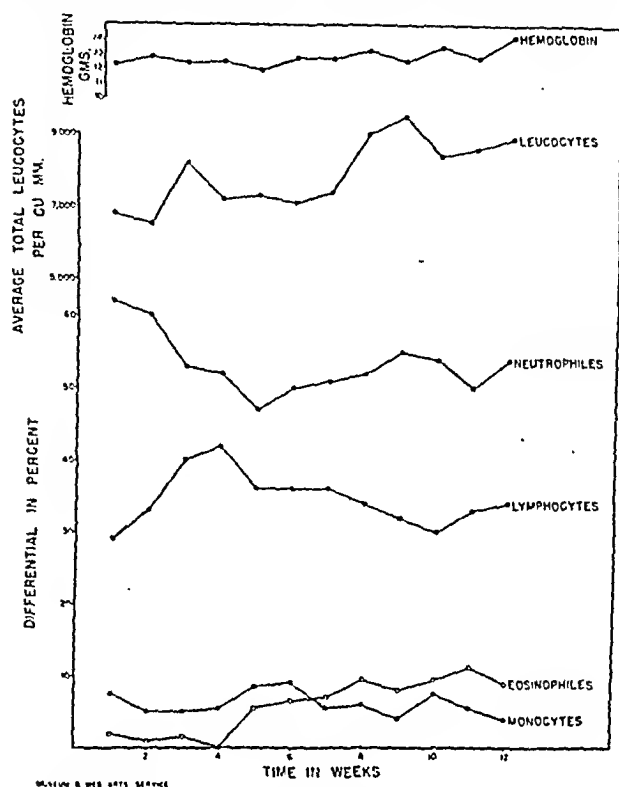


CHART 11.—Trends in average total leukocyte count, differential and hemoglobin in Chinese patients who had Roentgen evidence of bronchopneumonia.

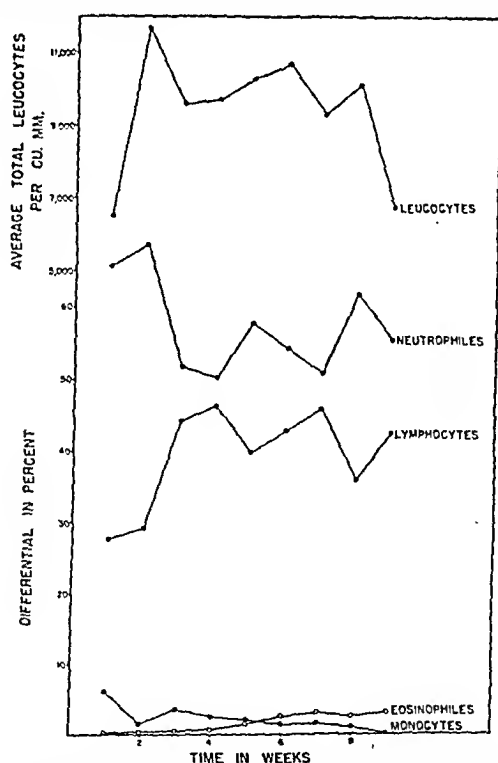


CHART 12.—Trends in average total leukocyte count and differential in American patients. Eosinophilia is less marked than in Chinese but is nevertheless definite.

In the American patients a leukopenia was present during the 1st week of the disease; however subsequently a mild leukocytosis developed and this persisted until the end of the 8th week. The trends in the differential and in the hemoglobin were similar to those in the Chinese (Chart 12, Table 12):

TABLE 12.—FORMED ELEMENTS OF PERIPHERAL BLOOD IN UNCOMPLICATED CASES (AMERICAN)

Week of disease	Average leukocyte count	Differential (%)				Hb. (gm.)	No. of cases
		Neut.	Lymphs.	Mono.	Eosin.		
1 . .	6,545 (3800-8800)	65.4 (50-79)	27.2 (17-42)	6.0 (0-15)	0.1 (0-2)	16.1 (12.5-17.5)	10
2 . .	11,750 (8700-18,350)	68.6 (51-87)	29.0 (12-45)	1.7 (0-11)	0.4 (0-2)	15.0 (11.5-18.0)	18
3 . .	9,700 (5800-19,000)	51.5 (34-76)	44.4 (24-62)	3.2 (0-12)	0.6 (0-3)	15.0 (12.0-18.0)	19
4 . .	9,760 (5600-16,550)	50.1 (26-72)	45.9 (27-70)	2.1 (0-14)	0.8 (0-5)	14.5 (13.5-15.0)	16
5 . .	10,390 (6500-15,450)	57.1 (45-71)	39.6 (23-51)	2.0 (0-6)	1.3 (0-2)	14.2 (12.5-15.0)	10
6 . .	10,745 (7400-15,950)	54.1 (40-68)	42.3 (30-55)	1.1 (0-3)	2.5 (0-10)	14.0 (12.5-15.0)	10
7 . .	9,300 (6850-12,400)	50.5 (35-77)	45.5 (19-58)	1.1 (0-5)	3.0 (0-12)	13.2 (12.5-14.0)	8
8 . .	10,110 (7500-12,600)	61.2 (52-72)	35.2 (26-45)	0.8 (0-2)	2.6 (0-9)	12.5 (12.0-13.0)	5
9 . .	6,780 (6200-11,050)	55.0 (43-67)	42.4 (31-57)	0 ..	3.0 (0-7)	14.5 (14.0-15.5)	5

TABLE 13.—VALUES FOR BLOOD UREA NITROGEN IN PATIENTS WITH AZOTEMIA

Case No.	Day of disease admitted	Duration of fever (days)	B.U.N. (mg. per 100 cc.) (days of disease in parentheses)	Abnormal urinary findings
3 . . . . .	7	19	63, 52, 24, 16, 8 (16, 20, 24, 26, 35)	+
5 . . . . .	7	24	20, 25, 25, 18, 11 (14, 16, 20, 24, 27)	+
7 . . . . .	9	36	17, 23, 15, 8 (14, 16, 15, 24)	+
8 . . . . .	8	Died on 16th day	28, 50, 108 (11, 12, 16)	+
13 . . . . .	11	26	23, 30, 30, 31, 13 (11, 14, 18, 21, 24)	+
18 . . . . .	15	20	32, 16, 14 (20, 29, 40)	+
20 . . . . .	6	16	25, 10 (9, 17)	+
22 . . . . .	Onset in hospital	20	71, 45, 13 (11, 16, 23)	+
30 . . . . .	9	23	25, 26, 8 (12, 15, 23)	0
33 . . . . .	7	23	17, 26, 40, 38, 15 (8, 12, 16, 19, 23)	+
34 . . . . .	5	18	20, 28, 25, 12 (6, 9, 13, 16)	+
37 . . . . .	12	19	21, 13, 8 (13, 18, 21)	+
38 . . . . .	7	16	18, 27, 12 (8, 11, 15)	+
41 . . . . .	8	26	34, 18 (13, 23)	+
42 . . . . .	8	17	13, 22, 25, 30, 9 (11, 15, 16, 21, 29)	0
46 . . . . .	7	10	32, 15, 11 (9, 11, 19)	0

23. AZOTEMIA. Of the 40 Chinese patients, 13 manifested a mild to a moderate azotemia during the course of the fever (Table 13). This occurred during the 2nd and 3rd weeks of the disease and particularly in those patients in whom the fever was prolonged or in those in whom the illness was more intense. The azotemia bore no relationship to the presence or absence of bronchopneumonia.

Three of the Americans developed azotemia. This was most marked



in the patient (Case 42) who was semistuporous and had an increased cerebrospinal fluid pressure.

24. URINARY FINDINGS. Abnormal findings in the urine\* were detected in 19 of the Chinese and in 6 of the American patients. These occurred irrespective of azotemia but occurred in all except 3 of the patients who had azotemia. These findings consisted of albumin, coarse or fine granular and hyaline casts, leukocytes and occasionally R.B.C. (Table 14). Casts and albuminuria were the most constant findings in these cases. Their appearance was transient and occurred especially during the 2nd and 3rd weeks of the disease.

TABLE 14.—URINARY FINDINGS

Case No.	Duration of fever (days)	Day of disease urinary abnormality found	Albuminuria	Casts per low power field	Leukocytes per high power field	R.B.C. per high power field	Degree of azotemia
1	24	29	Plus 1	0	Many	0	0
2	18	11	Trace	10-15 coarse gran.	0	0	
		14	Trace	1 coarse gran.	Occ.	0	0
		17	Plus 1	2-3 coarse gran.	0	0	
3	19	9	Plus 1	1-2 coarse gran.	0	0	
		12	Plus 2	1-2 hyaline; 1-2 granular	Occ.	0	Plus 3
		15	Plus 1	Many coarse gran.	0	0	
5	24	14	Plus 2	1-3 granular	0	Occ.	
		16	Plus 4	Mod. hyaline, many coarse gran.	Occ.	20-40	Plus 1
6	16	11	Plus 1	Numerous hyaline, occ. red blood cell cast	10-15	1-2	0
8	Died 16th day	10	Plus 1	4 granular moderate	Occ.	0	Plus 4
		12	Plus 2	Coarse granular	0	0	
10	16	6	Plus 1	Mod. coarse gran.	0	0	0
12	24	5	Plus 2	1-2 waxy rare gran.	5-10	1-2	Plus 2
13	26	12	Plus 1	2 coarse granular	3-6	0	Plus 1
19	21	14	Trace	1-2 granular	Occ.	0	0
20	16	21	Trace	Occ. hyaline	0	0	Plus 1
22	20	8	0	2-3 granular	0	0	Plus 4
		14	Trace	2-4 granular	0	0	
28	17	11	Plus 1	10-15 granular	Occ.	0	0
32	24	17	0	5 granular	3-4	0	0
33	23	7	Plus 1	6-8 fine granular	0	0	Plus 3
		9	Trace	Few granular	0	0	
		16	Plus 2	15-20 granular	3-5	0	
34	18	6	0	2 granular	3-4	0	Plus 1
		13	Plus 1	12-15 granular, few hyaline	0	0	
35	19	13	0	4-5 granular	3-4	0	Plus 1
		18	Plus 2	15-20 coarse gran.	2-4	0	
37	16	9	Plus 2	2-3 granular	6-8	0	0
38	16	8	Plus 2	12-15 granular	3-5	0	Plus 1
41	26	9	Plus 2	Many hyaline, many fine granular	0	0	Plus 2
50	19	8	Plus 2	2-3 granular	0	0	0
		12	0	Occ. fine granular	0	0	
51	24	11	Plus 1	Occ. fine granular	0	0	0
		13	Trace	6-8 granular	0	0	
		27	0	Few granular	0	Occ.	
54	12	7	Trace	Occ. hyaline	0	0	
		18	0	3 granular	3-5	0	0
55	14	6	Trace	Occ. coarse granular	5-16	1-2	0
57	18	7	0	1-2 fine hyaline	Occ.	0	
		12	Plus 1	8-10 fine hyaline	Occ.	0	0

25. COMPARISON OF THE MORE COMMON CLINICAL FINDINGS AND OXK TITER IN PATIENTS WITH AND WITHOUT PRIMARY ULCER. With the single exception of the OXK titer already commented on,

\* A number of samples of urine were checked by Capt. C. F. Kay of the Cardio-renal Section.

the patients with primary ulcers did not show important difference when compared to the group without ulcers. The incidence of rash, splenomegaly, lymphadenopathy and eye-ground changes as well as the duration of fever was approximately the same in both groups (Tables 15 and 16).

TABLE 15.—CLINICAL FINDINGS AND OXK TITER IN CHINESE PATIENTS WITH PRIMARY ULCER

Case No.	Day of disease admitted	Duration of fever (days)	Splenomegaly	Generalized lymphadenopathy	Eye-ground changes	Rash	Highest OXK titer
1 . . . . .	11	24	+	+	+	+	1/400
2 . . . . .	8	18	+	+	+	—	1/200
8 . . . . .	8	Died on 16th day	+	+	0	+	Not pos.
14 . . . . .	9	14	+	+	+	+	1/400
15 . . . . .	8	24	+	+	+	—	1/400
18 . . . . .	15	20	+	+	+	—	1/25
20 . . . . .	6	16	+	+	+	—	1/100
21 . . . . .	5	12	0	+	0	—	1/1600
22 . . . . .	—4	20	+	+	+	0	1/1600
23 . . . . .	10	19	+	+	0	—	1/100
24 . . . . .	9	19	+	+	0	—	1/100
25 . . . . .	16	26	+	+	0	—	1/200
28 . . . . .	9	17	+	+	+	—	1/400
29 . . . . .	8	15	+	+	+	+	1/200
30 . . . . .	9	23	+	+	+	—	1/6400
31 . . . . .	4	20	+	+	+	+	1/100
32 . . . . .	4	24	+	0	0	+	1/400
33 . . . . .	7	23	+	+	+	+	1/1600
34 . . . . .	5	18	+	+	0	+	1/400
35 . . . . .	12	19	+	+	+	—	1/800
36 . . . . .	6	18	+	+	+	+	1/200
37 . . . . .	8	16	+	+	+	+	1/1600
38 . . . . .	7	16	+	+	+	+	1/800
39 . . . . .	4	16	+	+	+	—	1/800
40 . . . . .	12	27	+	+	0	—	1/1600

+ means present. 0 means none present. — means not present while in ward.

TABLE 16.—CLINICAL FINDINGS AND OXK TITER IN CHINESE PATIENTS WITHOUT PRIMARY ULCER

Case No.	Day of disease admitted	Duration of fever (days)	Splenomegaly	Generalized lymphadenopathy	Eye-ground changes	Rash	Highest OXK titer
3 . . . . .	7	19	+	+	0	+	1/100
4 . . . . .	9	23	+	+	+	—	1/800
5 . . . . .	7	24	+	+	+	—	1/200
6 . . . . .	4	18	+	+	+	—	1/50
7 . . . . .	9	36	+	+	+	+	1/200
9 . . . . .	—4	11	+	+	+	+	1/200
10 . . . . .	5	16	+	+	+	+	1/100
11 . . . . .	10	21	+	+	+	—	1/25
12 . . . . .	3	24	+	+	+	+	1/200
13 . . . . .	11	26	0	0	+	+	1/100
16 . . . . .	2	20	+	+	0	+	1/200
17 . . . . .	5	18	0	+	+	—	1/50
19 . . . . .	6	21	+	+	+	—	1/200
26 . . . . .	7	12	0	+	+	—	1/200
27 . . . . .	7	14	+	+	0	—	1/50

+ means present. 0 means absent. — means not present while in ward.

26. MORTALITY. In this series of 64 patients, only 1 death occurred. This patient was a Chinese (Case 8) who appeared to be doing well except for a rapidly rising blood urea nitrogen. On the 16th day of his disease he developed a generalized convulsion, became comatose, and went into shock. Lumbar puncture revealed a cerebrospinal fluid pressure of zero. Despite intensive measures directed against shock the patient died 3 hours later after 3 more generalized convulsions.

27. TREATMENT. The treatment employed in this series of patients was essentially symptomatic and supportive.

General measures included complete bed rest and an adequate intake of fluid and calories in readily assimilable form. Fluid was supplied by vein only if the patient could not take it by mouth. Each patient received in addition 2 brewer's yeast tablets, 7 gr. of sodium chloride and 25 mg. of ascorbic acid 3 times each day. Supplements of sweetened diluted canned milk were given to the Chinese patients between meals.

Other therapy included oxygen inhalation if cyanosis was present, blood transfusion if in shock, and adequate sedation when indicated. We believe death in 1 patient with an increased cerebrospinal fluid pressure may have been prevented by spinal drainage.

Sulfadiazine was administered to 10 patients with and without bronchiopneumonia without detectable benefit. The dosage employed was 4 gm. as an initial dose and 2 gm. every 4th hour for 4 to 5 days. Neoarsphenamine (0.6 gm.) was administered to 2 patients early in the course of the disease without noticeable benefit. Convalescent blood, with a high titer (1/3200) against proteus OXK antigen was administered 5 days after onset of the fever to 2 patients but did not appear to influence the course of the disease in the amounts given (500 cc.). Many of the patients had had quinine or atabrine prior to and even after admission to the hospital without detectable effect on the course of the disease.

Since some of the patients had the primary lesions on the skin excised for biopsy and other studies, it was thought worth-while to compare the course of the disease in this group with that in which the ulcer was allowed to remain in order to see whether or not the excision of the primary focus shortened the subsequent course. It did not. The average duration of the fever was longer in the group that had the ulcer excised.

**Summary.** Clinical and laboratory data are presented on a series of 24 American and 40 Chinese patients who had a disease which appeared to be identical with tsutsugamushi or Japanese river fever, also called mite or "scrub" typhus. These data include observations on the temperature, pulse, blood pressure, rash, primary eschar, eye-grounds, and on the incidence and duration of splenomegaly and regional and generalized lymphadenopathy. Severe pulmonary, cerebral and cardiac symptoms are described as well as other complications. The laboratory data include the results of periodic total and differential white blood cell counts, hemoglobin and blood urea nitrogen determinations and urinalyses. The nature and duration of positive Weil-Felix reaction (proteus OXK) are described and a difference between the OXK titer in patients with and without primary ulcers is pointed out. Early in the disease, interesting eye-ground changes were observed, these persisted into convalescence. Azotemia was noted during the 2nd or 3rd weeks of fever. One of the patients in the series appeared to undergo a true relapse. The mortality in the series was 1.5%.

## REFERENCES

1. BOYD, J. S. K.: J. Roy. Army Med. Corps, 65, 289, 361, 1935.
2. CORBETT, A. J.: Bull. U. S. Army Med. Dept., 70, 34, 1943.
3. DOWDEN, R.: Indian Med. Gaz., 50, 208, 1915.
4. FLETCHER, W., and LESSLAR, J. E.: Bull. Inst. Med. Res., F.M.S., No. 2, 1925.
5. HEILIG, R., and NAIDU, U. R.: Indian Med. Gaz., 77, 338, 1942.
6. LEWTHWAITE, R., and SAVOOR, S. R.: Brit. J. Exp. Path., 17, 1, 448, 461, 1936.

## ON THE TOXICITY OF STREPTOTHRICIN

BY GEOFFREY RAKE, M.D., B.S.

DOROTHY HAMRE, PH.D.

FREDERICK KAVANAGH, PH.D.

WALTER L. KOERBER, PH.D.

AND

RICHARD DONOVICK, PH.D.

NEW BRUNSWICK, N. J.

(From the Division of Microbiology of The Squibb Institute for Medical Research)

STATEMENTS on the toxicity of streptothricin<sup>6</sup> have been published by Robinson and his co-workers. Thus Robinson<sup>4</sup> working with material of low potency (5 to 50 units per mg.) showed that the 5 unit material was of very low toxicity on a weight basis and 5 gm. (25,000 units) per kilo produced no evidence of toxicity when administered intravenously. However, the more potent material (by this is presumably meant the 50 unit material) was toxic intravenously at 50 mg. (2500 units) per 20 gm. mouse or 125,000 units per kilo. Some evidence of toxicity occurred at 50,000 units per kilo but no deaths. There appeared to be a relation between toxicity and rate of injection. At doses approaching the lethal dose mice collapsed with apparent respiratory failure and would appear dead. Respiration would finally recommence and return to normal within an hour. Intraperitoneally 60 mg. per mouse (150,000 units per kg.) produced toxic signs in 10 to 15 minutes that might persist for 24 hours, although the mouse eventually recovered. In these studies all observed deaths took place within 24 hours.

In a later paper<sup>3</sup> Robinson and his co-workers used aqueous solutions of material varying in potency from 5 to 300 units per mg. Mice (CFI albinos 18 to 21 gm.) were treated by various routes with a single dose and then observed for 5 days. When administered intravenously 60,000 units per kg. produced some deaths, but there was no effect by oral or subcutaneous routes. However, the authors' published figures show that the LD<sub>50</sub> (dose lethal for 50% of animals) by the intravenous and subcutaneous routes was almost identical (between 185,000 and 200,000 units per kilo). Orally 250,000 units per kg. were tolerated without effect but at 500,000 units per kg. anorexia and loss of weight developed and 10% of the mice died. In a still later paper<sup>5</sup> these same authors tested the toxicity of streptothricin by the sub-

cutaneous route. The  $L_{D50}$  obtained was approximately 3100 units per 20 gm. mouse or 155,000 units per kg. Deaths occurred on the 6th, 7th and 9th days.

**Technique.** In this work, Swiss mice weighing 19 to 21 gm. were used. Most inoculations were by the intravenous route using 0.5 ml. volume, but some groups received material subcutaneously, intramuscularly, intraperitoneally or by mouth. All animals which survived were observed for at least 21 days. Autopsies were performed on all those which died, except those dying during the night (when postmortem changes might influence the results). Portions of liver, spleen, pancreas, adrenal, kidney, voluntary muscle, heart, duodenum, jejunum, ileum, colon, cerebrum, cerebellum and medulla, and after subcutaneous inoculation, the site of infection, were taken for microscopic examination. They were fixed in Zenker's fluid and stained with eosin-methylene blue. Kidneys and some other tissues were also stained with Weigert's fibrin stain.

**Material.** The streptothricin to be tested varied in potency from 84.5 to 529 units per mg. The latter material represents a highly purified product regenerated from a crystalline derivative.<sup>2</sup> In addition, one fraction, obtained during the purification process but without any antibiotic activity, was tested. The unit of activity is not an absolute but rather a reference unit and corresponds to the unit of Foster and Woodruff.<sup>1</sup> Activity of a given preparation has been ascertained by comparison with a standard, tested at the same time and under the same conditions, which standard had a given value in reference units. This value in reference units had been obtained by comparison with a sample of streptothricin of given potency in reference units kindly supplied by Dr. J. W. Foster of Merck & Co., Inc.

**Results.** In most cases only small quantities of material were available and only few mice at one or two concentrations could be tested. It soon became apparent that following intravenous inoculation two types of toxic reaction occurred. The first was apparent immediately following or even during inoculation. The mice would run for a few steps and then collapse. Breathing became very labored and then ceased. In some cases the mice died and in others they recovered completely within a few minutes. The second type of reaction began to appear about 24 hours after inoculation or might be more delayed. The mice became listless, anorexic, and the fur was ruffled. Breathing was labored, and the animals often sat back on their hind legs for long periods and showed a tendency to fall backwards. Death followed quietly, although on rare occasions there were convulsions, occurring anywhere from the 2nd to the 12th day after inoculation, and from 1 to several days after the animals became sick. Most of the deaths occurred before the 8th day and 22% on the 6th day. If a record was kept of the amount of food eaten by the mice for each 24 hour period, the consumption was found to decrease markedly during the 2nd day in the mice receiving the largest doses. In those receiving doses small enough to cause few if any deaths, this decrease in consumption occurs on the 5th day. This anorexia seems to be a prime symptom and often precedes the appearance of any other marked malaise.

When these two types of toxic reaction were examined in relation to the type of material used in the toxicity experiments, certain points were noted. Thus the mortality rate of delayed deaths is related to

the number of units of streptothricin inoculated and not to the purity or any other characteristics of a given batch of material. It would seem, therefore, to be due to the streptothricin. On the other hand, the rate of acute deaths bears little relation to the number of units of streptothricin inoculated (Table 1). It does, however, bear a definite relation to the purity of a given batch of material. Thus (Table 2) the least pure sample tested—ST1121 84.5 units per mg.—killed immediately all mice receiving doses of 375, 458 and 1146 units intravenously while the purest preparation of streptothricin killed immediately only 1 mouse of 4 receiving 2630 units intravenously and none of those receiving 2296 units, 1766, 1322 and so on down to 88 units. It is clear from this that acute deaths can be produced with highly purified material, but only with very large doses intravenously (132,480 units per kg.). From these results it would seem that, for the most part, the acute deaths were due to impurity other than streptothricin. The nature of the acute deaths resembles closely those produced by histamine and related substances.

TABLE 1.—COMBINED INTRAVENOUS TOXICITIES OF ALL SAMPLES OF STREPTOTHRICIN TESTED

Dosage (units)	Immediate toxicity		Delayed toxicity	
	No. of mice	Mortality (%)	No. of mice	Mortality (%)
3000-4140 . . . .	6	100.0		
2500-3000 . . . .	41	56.1	18	88.9
2000-2500 . . . .	35	25.7	26	92.3
1500-2000 . . . .	37	27.0	27	85.2
1000-1500 . . . .	45	17.8	20	89.2
88-1000 . . . .	77	20.8	61	50.8

The mice observed for delayed toxicity represent, of course, those surviving the immediate reaction.

The detailed results on 4 materials, of which sufficient was available to test in a moderate number of mice, are shown in Table 2. It is seen that the amount in units required to kill immediately decreases with decreasing potency (and purity). Thus the approximate immediate  $L_{D50}$  for S326-3273 (pure streptothricin) is >2630 units, for 95K (330 units per mg.) is 2400 units, for 125K (250 units per mg.) is 1728 units, and for ST1121 (84.5 units per mg.) only 286 units. On the other hand, the  $L_{D50}$  for delayed deaths occurs at more nearly the same level for the purest material and for the least pure. Streptothricin, or at least the impure material, is also toxic by routes of administration other than intravenous. However, the delayed toxicity is considerably less by these other routes (stomach tube, subcutaneous, intramuscular and intraperitoneal injection), and no immediate deaths, or indeed any reactions, occur after administration by these routes (Table 2).

**Pathologic Changes.** That the material, when given intravenously, has a marked effect on the blood-vessels can be observed even in the living animal. Thus, even after the administration of purified material, in most of those mice which survive for 24 hours or longer marked gangrene of the tail develops distal to the point of intravenous inocula-

tion and this part of the tail is eventually lost. In addition, hemorrhages may occur in the skin and are particularly noticeable in the ears. Following subcutaneous inoculation, inflammation occurs at the site of injection.

TABLE 2.—TOXICITY OF SAMPLES OF STREPTOTHRICIN OF VARYING POTENCY

Route of inoculation	Dosage (units per mouse)	Immediate deaths	Delayed deaths
ST1121—84.5 units per mg.			
IV . . . . .	1146	4/4	
	458	5/5	
	375	5/5	
	286	5/10*	2/5
	228	0/10	4/10
95K—330 units per mg.			
IV . . . . .	4106	3/3	
	2933	9/10	1/1
	2567	8/10	2/2
	2281	4/10	6/6
	2053	0/10	10/10
OS . . . . .	1027	0/18	5/18
IM . . . . .	977	0/20	2/20
125K—250 units per mg.			
IV . . . . .	1997	3/3	
	1810	5/10	4/5
	1498	2/9	5/7
	998	1/6	5/5
	499	0/1	1/1
IP . . . . .	1810	0/8	1/8
S326-3273—529 units per mg.			
IV . . . . .	2630	1/4	3/3
	2296	0/1	1/1
	1766	0/4	4/4
	1322	0/4	4/4
	882	0/4	2/4
	661	0/4	2/4
	441	0/4	1/4
	220	0/4	1/4
	88	0/4	0/4
STCP—102 units per mg.			
SC . . . . .	4500	0/6	5/6
	2250	0/10	2/10
	1125	0/10	0/10
	563	0/10	0/10

\* Five mice died out of 10 inoculated.

IV = intravenous; OS = by stomach tube; IM = intramuscular; IP = intraperitoneal; SC = subcutaneous.

On autopsy the mice were always found emaciated. Apart from occasional grossly observable areas of necrosis in the liver the only changes seen were in the small intestine or in the kidney and abdominal wall following subcutaneous inoculation. The small intestine was often filled with blood or might be so friable as to rupture very readily.

*Microscopically* the lesions produced by intravenous inoculation varied somewhat with different batches although certain lesions were found with all batches. There seemed to be no significant difference

in the tissue changes produced by material of different potency. The most striking lesion occurred in the small intestine. Damage was found in the duodenum, jejunum or ileum. In what appeared to be the early changes the submucosa and lamina propria were edematous or thickened, and there was marked monocyctic infiltration. The tips of the mucosal villi might be necrotic. In other cases the earliest lesion appeared to be marked hemorrhage into the wall of the intestine and escape of blood into the lumen of the gut. More extreme lesions, which appeared relatively frequently, were on the one hand intussusception and on the other complete gangrene of the intestinal wall. In all, 16 out of 23 mice examined showed one or other of the above lesions, most of them to an extreme degree.

Another severe lesion was not as frequent. This was an arteritis which occurred in medium or small arteries in the lung, pancreas, heart or kidney. The media was necrotic and Weigert's stain showed marked disruption of elastic fibers. The adventitia contained fibrin, red cells, leukocytes and monocytes. This lesion was found in 6 mice. Four others showed foci of necrosis in the heart muscle with hemorrhage and cell infiltration.

In many cases (12 mice) the lungs showed areas with fluid and blood in the alveoli. In the kidney there were different degrees of tubular damage with hyaline or amorphous casts in some tubules. In 3 cases there were areas of necrosis in the liver and in 3 others necrosis of neurones was observed in the hippocampus or in the medulla.

Colon, spleen, salivary glands, lymph nodes, adrenals and bone marrow appeared normal.

In mice dying after subcutaneous injection of streptothricin (see Table 2, Lot STCP) the pathologic picture was entirely different. Macroscopically, as noted above, there was an area of thickening and inflammation surrounding the point of inoculation in the abdominal wall. Apart from this, the only other gross change was that noted in the kidneys which were usually large and pale, and might (in 2 cases) show advanced hydronephrosis. Microscopically, the site of inoculation showed an intense inflammation in the subcutaneous tissue reaching down to the subjacent muscle. The overlying epidermis was greatly thickened, as was the corium. There was an infiltration of fibroblasts and monocytes with occasional binucleated giant cells. Scattered polymorphonuclear leukocytes were not frequent but collections of them were observed forming small or even extensive abscesses. In 1 case such abscesses appeared to be starting around blue-staining, jagged foreign bodies apparently crystalline in nature, but these could not be found in any of the 5 other preparations examined. The intensity of the inflammatory reaction varied but slightly from 1 mouse to another. The kidneys showed quite extensive tubular damage with many hyaline and granular casts. In 1 case, as noted macroscopically, there was advanced bilateral hydronephrosis and in another case unilateral hydronephrosis. In still a third instance, a unilateral dilatation of the pelvis was obvious in the microscopic preparations, although it had not been noted in the gross examination.



**Summary.** Streptothricin varying in potency from approximately 16% of purity to almost completely purified material has been tested for toxicity in mice by various routes. When the intravenous route is used it is found that the toxic phenomena can be divided into those which occur immediately, and which appear to be due to impurity with a histamine-like activity, and those which come on later and lead to death 2 to 12 days after inoculation. Since the  $L_{D50}$  in units of streptothricin for these delayed deaths does not vary markedly with different preparations from the least to the purest, it is presumed that they are due to the streptothricin itself. Symptoms in the mice include anorexia, labored breathing and, rarely, convulsions.

In those mice which died following intravenous inoculation, lesions were found in the small intestine and in many cases the whole intestinal wall was gangrenous. Other important lesions were an acute arteritis and myocarditis, tubular lesions in the kidney and occasional lesions in the central nervous system and liver. Following subcutaneous inoculation, apart from the local reaction in the abdominal wall at the site of inoculation, the lesions found were confined to the kidney and were considerably more marked in this organ than those noted in mice which had been inoculated intravenously.

Our thanks are due to Dr. J. Fried and Dr. O. Wintersteiner of the Division of Organic Chemistry of The Squibb Institute for Medical Research for the preparations used in these studies.

#### REFERENCES

1. FOSTER, J. W., and WOODRUFF, H. B.: J. Bact., 45, 408, 1943.
2. FRIED, J., and WINTERSTEINER, O.: To be published.
3. ROBINSON, H. J., GRAESSLE, O. E., and SMITH, D. G.: Science, 99, 540, 1944.
4. ROBINSON, H. J.: Rutgers Thesis, 1943 (unpublished).
5. SMITH, D. G., and ROBINSON, H. J.: Proc. Soc. Exp. Biol. and Med., 57, 292, 1944.
6. WAKSMAN, S. A., and WOODRUFF, H. B.: Proc. Soc. Exp. Biol. and Med., 49, 207, 1942.

### KLEBSIELLA PNEUMONIAE BACTERIEMIA SUCCESSFULLY TREATED BY PENICILLIN\*

BY COMD'R J. LESTER KOBACKER, (MC) USNR

AND

LT. COMD'R G. BURCH MEHLIN, (MC) USNR  
USN BASE HOSP. 7, FLEET POST OFFICE, SAN FRANCISCO, CALIF.

INFECTIONS with *Klebsiella pneumoniae* (Friedländer's bacillus) always have been regarded as serious, and with good reason. Statistics reveal mortality figures of 35 to 97% for various types of the infection, including both bacteriemic and non-bacteriemic cases. At one time bacteriemia represented an almost certain fatal outcome, as witness Solomon's<sup>13</sup> series in 1937 and Bullowa's<sup>2</sup> statistics of the same year which revealed 100 and 92% respectively. Later figures were somewhat lower, 75 to 85%, possibly due to the aid of sulfadiazine

\* The opinions and assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

and sulfapyridine. The experimental studies of the effects of these drugs on animals<sup>1,4</sup> suggest that they may actually exert some curative effect, sulfadiazine being the more potent. However, with mortality figures so appalling, any therapy which might aid in the conquest of this infection should be given adequate trial, without prejudice, and the results made known.

The use of new antibiotic agents in the treatment of infections is undergoing numerous radical modifications. Initial concepts concerning dosage have been revised with consequent changes in the reported effectiveness of the drugs. Penicillin was reported ineffective in the treatment of subacute bacterial endocarditis on the basis of early dosage schedules;<sup>10</sup> yet recent reports indicate a hitherto never-achieved arrest of cases when massive dosage has been applied.<sup>9</sup> The growing literature on penicillin bears constant testimony to the variation in methods of administration, frequency of dosage and other features which must be given firm basis only through the clinical experience of many workers.

It has been a customary and quaint procedure for many writers to classify bacterial response to therapy in accordance with the organisms' acceptance or non-acceptance of the Gram stain. This concept is to be found along with certain other antiquated dicta in many textbooks. Now again, as in the days of enthusiasm for the use of intravenous dyes, we find bacteria being segregated in accordance with this unsupported thesis. The staining property of bacteria neither confers pathogenicity on them nor does it affect their vulnerability. Hence we must regard with some suspicion such far-reaching precepts as appeared this year when Schmitt<sup>11,12</sup> listed as "insusceptible" to penicillin all gram-negative bacilli, including the *Klebsiella pneumoniae*. Basing the viewpoint only on Fleming's monumental experimental laboratory work<sup>6</sup> and on that of Hobby, Meyer, and Chaffee,<sup>7</sup> and to our knowledge, on no clinical experience, these and other articles gave rise to a new tradition. In a recently published A. M. A. guide<sup>14</sup> to the uses of penicillin, based on the similar list of Dawson *et al.*,<sup>3</sup> under a main heading, "Not Established as Effective for," and a sub-heading: "All Gram negative bacillary infections" there was listed this full group, including *Klebsiella pneumoniae*.

In the light of this, it seems desirable to present a case of *Klebsiella* bacteriemia treated by penicillin with what, we deem, were dramatic results.

**Case Report.** A Merchant seaman, 32 years old, was admitted Aug. 23, 1944, to a U. S. N. Base Hospital in the South Pacific in deep coma. No history was obtainable except that he was in another hospital 2 weeks earlier under the diagnosis of "acute catarrhal fever" and that he had complained of feeling ill the day preceding admission. There was an indefinite report of his having been seen taking some tablets at bedtime and he was discovered unconscious in the morning.

**Physical Examination.** Temp. 103° (axillary). The patient was intensely cyanotic. His breathing was rasping, uneven, and 26 per minute. There was no response to any stimulation. The pupils were small but not pinpoint. The nose showed a crusted purulent discharge. The teeth were dirty and

poorly repaired. The throat was diffusely reddened and there was a swelling in left posttonsillar area. The examination of the heart and lungs was negative but breathing was noisy because of transmitted upper tract mucous rattles. The blood pressure was 138/72. There was a long, left flank scar (later found to be due to exploration after a stab wound). The neurologic examination was negative and all other physical findings were within normal limits.

*Laboratory Data.* Hb., 85%; R.B.C., 4,500,000; W.B.C., 34,000 (neutrophils, 86%; lymphocytes, 12%; eosinophils, 1%; basophils, 1%). Urine: yellow, clear; sp. gr., 1.023; albumin, 0; sugar, 0; micro., occasional leukocyte. Thick smear for malaria, negative. Spinal fluid, pressure 177 mm. of water, clear, colorless. Cell count, 0. Pandy's test, negative. Smear and culture, negative. Chest Roentgen ray, elevation of the right diaphragm. Clear lung fields.

Constant oxygen administration by mask was employed from the time of entry for 48 hours. Two hours after admission, an effort was made to pass a nasal tube to obtain a specimen of the gastric contents. An obstruction was encountered and severe laryngospasm occurred, during which pus appeared in his mouth and on turning him face down several ounces of thick stringy pus poured from his nose and mouth. The passages were cleared by aspiration and a clear view of the throat was obtained. There was a small opening in the swelling behind the left tonsil at the lateral border of the posterior pharyngeal wall. From this pus was escaping.

A blood culture was taken after which he received 5 gm. of sodium sulfadiazine intravenously.

The course from this point is indicated by the following notations:

8-23-44: 2100—Temp., 105.4° (rectally). Respirations, 36. Pulse, 150. Condition grave. Fundi—haziness of both nasal disk margins. Very restless.

2300—Penicillin therapy begun (200,000 International units in 1000 cc. 5% glucose in saline given by intravenous drip). Thereafter for 82 hours a continuous intravenous drip of penicillin was maintained introducing about 300,000 units in 24 hours. Each 100,000 units was dissolved in 1000 cc. of 5% glucose in saline.

8-24-44: 0800—Respiration, 50. Pulse, 160 and very thrready. Skin cyanotic and mottled. Extreme restlessness. Fundi: disk elevation on left, and increase in haziness of nasal disk border on the right. Slight palpebral edema.

1200—A report from the laboratory at this time identified a blood culture growth as *Klebsiella pneumoniae* (Friedländer's bacillus).

Despite the previously mentioned tradition that penicillin was an ineffective agent *versus* *Klebsiella*, it was determined to continue the full dosage. The patient's condition appeared desperate.

1500—Color slightly improved. Temp., 102.6° (axillary); pulse, 144; respiration, 48.

8-25-44: 0700—Had a very restless night despite nembutal per rectum. Catheterized at 12-hour intervals.

0900—Temp., 103.4° (axillary); pulse, 160; respiration, 32 to 40. Condition worse. Restlessness had resulted in numerous large blisters on the legs, back and buttocks. Spinal fluid, clear, colorless; pressure, 140 mm. of water; laboratory examinations of fluid all negative.

0930—Sodium amytal, 0.3 gm., intravenously for extreme restlessness.

1803—Pentothal sodium, 0.5 gm., intravenously.

2050—Scopolamine, 0.6 mg. (The combination of barbiturate and scopolamine proved effective and was used during the ensuing 24 hours.)

8-26-44: 0600—Temperature had fallen steadily. Temp., 99.8° (axillary); pulse, 104; respiration, 28. Responded to stimuli. Swallowed water in sips.

0820—Marked involuntary diarrhea. Coughed and raised sputum.

2200—Slept quietly.

8-27-44: 0900—Temp., 99.4° (orally); pulse, 88; respiration, 30. This concluded the intravenous use of penicillin (1,200,000 units had been employed to this point and in a period of 82 hours). Cough continued.

*Roentgen ray* showed small area of consolidation at the left base.

From 8-27 to 8-28, 20,000 units of penicillin were given intramuscularly every 3 hours. From 8-29 to 8-30 the dose was 10,000 units every 3 hours and thereafter until 8-31 it was 10,000 units every 4 hours. The total amount of intramuscular dosage was 530,000 units and the entire amount employed was 1,730,000 units.

On the 4th day of hospital stay the optic nerve heads were normal to ophthalmoscopic view.

Residua such as the abrasions and blisters and the pneumonic area cleared promptly and the patient was ambulatory on his 11th hospital day.

A blood culture taken on the 2nd day of the penicillin therapy was negative. Smears from the abscess 1 day after its evacuation showed a mixed flora with scattered encapsulated gram-negative organisms morphologically *Klebsiella*. The final report on the initial blood culture was "*Klebsiella pneumoniae* or Friedländer's bacillus confirmed culturally and morphologically. Specific typing sera for Friedländer group was not available."

It was ascertained in the history obtained after the patient's recovery that he had felt very ill the night prior to admission, and had taken 4 or 5 sedative pills, size and nature unknown.

**Discussion.** The events in the clinical progress in this case were confused somewhat by the history of self-administration of a sedative. It is impossible, therefore, to judge whether complete coma was a *bona fide* feature of the infection. The sequence of events in the progress of the case indicates the initial focal point as the pharyngeal abscess, followed by bacteriemia and attendant, but later, pneumonia. Suspicion may well exist that an early cavernous sinus phlebitis was in progress at the time of admission. All fundus signs disappeared with improvement of the patient. Though *Klebsiella* bacteriemia is not uniformly fatal, especially if there is an accessible primary focus, the extremely rapid cessation of symptoms in a patient so critically ill inclines one strongly to the conclusion that the therapy exhibited had a marked effect. It must be borne in mind that penicillin exerts its action as a bacteriostatic only during bacterial multiplication. Gardner's work<sup>6</sup> revealed that morphologic changes occurred in the numerous types of bacteria tested and even in the group classified as gram-negative—a class which has been regarded as uniformly non-susceptible. In these last there was noted chiefly cellular elongation. It is not unreasonable to presume that bacteriostasis may reveal itself *in vivo* to be a critical factor, though the noted changes *in vitro* were insignificant. In 1943, Jaffe<sup>8</sup> concluded his report of extrapulmonary *Klebsiella* infections which recovered under treatment with sulfadiazine on a hopeful note. We quote his final sentence: "Because of a persistent high mortality rate in *Klebsiella pneumoniae* infections, it is felt that further therapeutic trials should be attempted with the newer sulfonamide compounds and also with the newer antibacterial agents such as gramicidin, penicillin and aspergillin."

With this presentation of a case of severe *Klebsiella pneumoniae* infection with bacteriemia treated successfully by penicillin, it is hoped that its further use in such conditions may be encouraged despite all previous dicta that the condition would not be responsive.

**Summary.** 1. A case of very severe infection with *Klebsiella pneumoniae* treated by large doses of penicillin recovered. A pharyngeal

abscess was the initial focus, bacteriemia complicated the condition, and there was probably early cavernous sinus phlebitis and a secondary bronchopneumonia.

2. This appears to be the first record of a case of *Klebsiella pneumoniae* infection treated by penicillin.

3. The penicillin was administered in direct contradiction to all published formulæ regarding susceptibility of this organism.

4. Since the notoriously fatal character of such infections is recognized, it is hoped that the rapid and dramatic recovery of this patient under penicillin therapy will encourage its further trial in large dosage in future *Klebsiella pneumoniae* infections.

#### REFERENCES

1. BLISS, E. A., FEINSTONE, W. H., GARRETT, A. W., and LONG, P. H.: Proc. Soc. Exp. Biol. and Med., 39, 12, 1938.
2. BULLOWA, J., CHESSE, J., and FRIEDMAN, N. B.: Arch. Int. Med., 60, 735, 1937.
3. DAWSON, M. H., HOBBY, G. L., MEYER, K., and CHAFFEE, E.: Ann. Int. Med., 19, 707, 1943.
4. FEINSTONE, W. H., WILLIAMS, R. D., WOLFF, M. S., HUNTINGTON, E., and CROSSBY, M. L.: Bull. Johns Hopkins Hosp., 67, 427, 1940.
5. FLEMING, A.: J. Path. and Bact., 35, 831, 1932.
6. GARDNER, A. D.: Nature, 146, 837, 1940.
7. HOBBY, G. L., MEYER, K., and CHAFFEE, E.: Proc. Soc. Exp. Biol. and Med., 50, 285, 1942.
8. JAFFE, S. A.: J. Am. Med. Assn., 122, 292, 1943.
9. KEEFER, C. H.: Report to Committee on Medical Research, O.S.R.D., May 1, 1944.
10. RICHARDS, A. N.: J. Am. Med. Assn., 122, 235, 1943.
11. SCHMITT, G. F.: AM. J. MED. SCI., 207, 661, 1944.
12. SCHMITT, G. F.: U. S. Nav. Med. Bull., 42, 1047, 1944.
13. SOLOMON, S.: J. Am. Med. Assn., 108, 937, 1937.
14. Statement on Penicillin by Council on Pharm. and Chem., J. Am. Med. Assn., 125, 707, 1944.

#### RICKETS IN ICELAND

BY NIELS DUNGAL, M.D.

REYKJAVIK, ICELAND

(From the Department of Pathology and Bacteriology, University of Reykjavik)

IN medical literature reference is sometimes made to Iceland as a country in which rickets is unknown. This is a misconception which may be traced back to Icelandic medical authorities from the 18th century, who have been quoted and misquoted ever since.

In a medical survey performed almost a century ago Schleisner<sup>2</sup> noted 7 patients with rickets among a total of 327 patients personally examined by himself. But as he does not mention their age, we cannot know how many of them were children, nor decide whether some of these cases have not been residual malformations after healed rickets.

The first systematic survey of prevalence of rickets was published by Thoroddsen,<sup>4</sup> who found rickets among the children of Reykjavik in 51.5% of children within 2 years of age. These investigations were founded on clinical examinations, and the author stated that undoubtedly the percentage of rickets was actually considerably higher.

There are still some practitioners in Iceland who doubt the conclusion of Thoroddsen's paper. This scepticism may probably be explained by the comparatively rare occurrence of rickets in its most extreme forms, as seen in the industrial cities of Europe. Many a

country doctor can practice for years without seeing such cases. On the other hand, nobody who keeps his eyes open on the streets of Reykjavik can fail to observe the frequency of malformed bones, particularly the legs, which around knees and ankles carry unmistakable signs of healed rickets.

**Material.** A total of 253 children were examined, all in Reykjavik, but 14 failed to appear for final examination, making a total of 239 completed examinations. All the children were from 3 months to 2 years of age. Of this number, 71 were from a health center for children, the remaining 168 were obtained by writing to mothers who had been delivered at the obstetric department of the State hospital in Reykjavik, encouraging them to bring the children to us and have them examined carefully for rickets. All these children were, with 2 exceptions, between 3 and 12 months of age. Most of the children from the health center were more than 1 year old.

**Methods of Examination.** Each child was stripped naked and examined clinically. A case history was taken at the same time and noted whether the child had received any antirachitic treatment. Of each child a Roentgen ray picture was taken of wrist and knee, and in all doubtful cases also of the ankle. As a rule, the changes were more distinct in the ankles than in the wrists. Of the young children, under 1 year of age, we took a picture of the whole crus on which knee and ankle joint could be seen with the entire leg bones. Such pictures were particularly valuable, as changes were frequently seen in the leg bones apart from the joints, particularly in the fibula.

The *clinical examination* was directed to the general condition of the child, noting state of nutrition, anemia, condition of muscles, and so forth, with special attention directed toward the condition of the bones:

1. The fontanelles were examined and if open, their size measured.
2. The cranial bones were examined bimanually. Changes were frequently found, especially in the form of extended flat prominences in the region of the parietal bones, very pronounced in some children. Flattening of the occipital bone and hairlessness at the back of the head was also frequently observed.
3. The chest was carefully observed, for here changes were frequently noted, chiefly in the form of a rachitic rosary and a Harrison's groove, both of which were comparatively frequent. Some children displayed major malformations of the thorax: barrel-shaped chest with flattened sides, of a more or less pronounced pectus carinatum, with protruding sternum.
4. Examination of extremities, with palpation of wrists and inspection, of possible curves of legs.

**Results.** The following table gives a survey of our clinical findings:

TABLE 1.—BONE FINDINGS

Age	Harrison's groove		Costochondral prominences		Parietal prominences	
	+	-	+	-	+	-
3 mos. . . . .	2	7	6	3	5	4
4 " . . . . .	1	3	2	2	3	1
5 " . . . . .	5	18	14	9	17	6
6 " . . . . .	16	12	21	7	21	7
7 " . . . . .	17	25	22	20	24	18
8 " . . . . .	3	1	2	2	2	2
9 " . . . . .	19	26	24	21	25	20
10 " . . . . .	12	9	10	11	12	9
11 " . . . . .	7	9	5	11	12	4
12 " . . . . .	1	..	1	..	1	..
1 yr. . . . .	1	44	3	42	12	33
2 yrs. . . . .	3	8	2	9	2	9
Totals . . . . .	57	162	112	137	136	113
Per cent positive . . .	36		44		54	

*Criteria for Clinical Rickets.* No single sign was considered sufficient for diagnosing rickets clinically, except Harrison's groove. Parietal prominences were not considered sufficient alone, but in combination with a flattened occipital bone or a distinct rachitic rosary were considered sufficient for diagnosing rickets. A distinct rachitic rosary was practically never the only sign of rickets. Parietal prominences and other changes in the cranium or chest could almost without exception be found in addition, to corroborate the diagnosis.

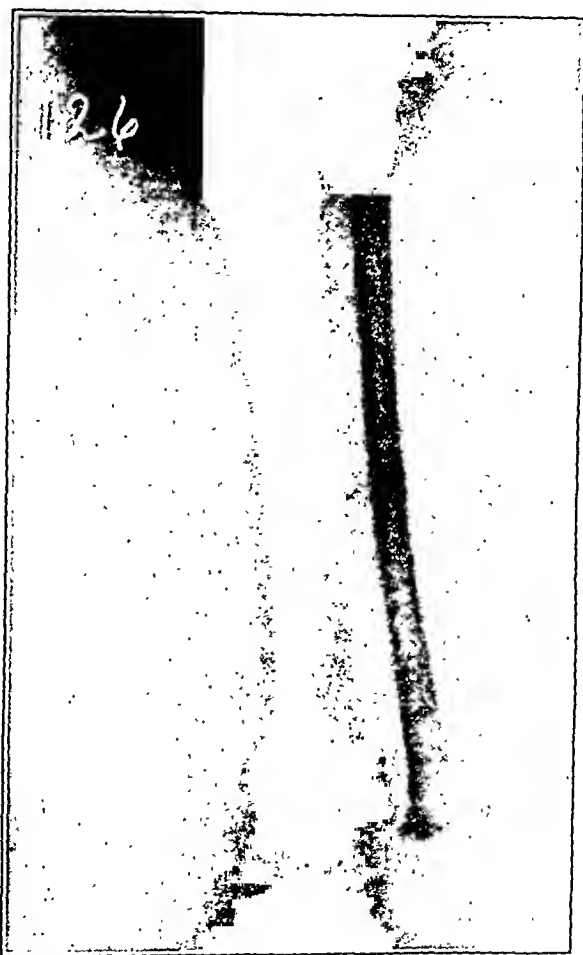


FIG. 1.—Crus from 5 months female. Pronounced rickets. Fibula curved inward. Lower end of tibia inclined inward, causing deformity (varus inclination) of talocrural articulation. Broadening of ossification line of tibia's lower end. Medial condyle of tibia drawn out into a point. Clinically: distinct Harrison's groove and rosary. The child had received no antirachitic treatment.

In a poorly nourished child with distinct signs of rickets we found a rachitic rosary of the special kind which is supposed to be characteristic of scurvy: a bayonet-shaped prominence of the costochondral junction, of such a form that a finger proceeding inward along the surface of the rib falls suddenly down on the cartilage.

In the extremities comparatively slight changes were found clinically. Epiphyseal thickenings, which are so frequently described elsewhere, were not found clinically by us, neither in the wrists nor in other joints.



FIG. 2.—Well calcified bones with straight ossification lines. No rickets. Child, 10 months old, had received vigantol and cod-liver oil for months.



FIG. 3.—Child, 6 months old. No antirachitic treatment. Distal end of ulna cup-shaped from calcium resorption. Calcium shadow clouded on ulna, but fairly distinct on radius.

Roentgen ray examinations were at first made of right wrist and left knee of each child. But we soon realized how valuable a picture of the ankle was, and added it in all doubtful cases where we had not taken a picture of the whole crus.



The Roentgen ray pictures were interpreted according to the findings described by Wimberger<sup>5</sup> and Lindblom.<sup>1</sup> Our principal criterion was the aspect of the line of calcification at the epiphyses: instead of the clear-cut, straight and narrow line of normally growing bone, the calcification line is seen more like an indistinct shadow, indented and broken and in severe cases no calcification can be seen, but only a broad band of uncalcified tissue, and at last the distal end of the bone becomes broader with a concave surface owing to absorption of calcium. Correspondingly and preceding these changes, the spongiosa network is blurred, owing to insufficient calcium content, and the diaphysis loses in strength and straightness, particularly in slender bones like the fibula of infants, which was frequently curved inward toward the tibia. In general the fibula seemed to calcify later and less than the tibia, and the ossification lines were always more indistinct in the fibula than the tibia, in all rachitic cases, although they were just as distinct in non-rachitic cases. This suggested that the bone which is less exposed to strain and exercise did receive less calcium than the one which had a more pronounced functional stress.

In the knees we observed changes of a characteristic appearance: at the medial articulate surface of the tibia the bone appeared to be broadened and flattened in such a way that the median condyle came to be drawn out into a point (Fig. 1). In some cases a similar formation was seen on the lateral condyle of the tibia, but rarely on the medial condyle of the femur. Probably these formations are due to compression of young cartilage and osteoid tissue which is presumably weakened by other reasons, particularly want of vitamin C, for such changes are considered a sign of scurvy.

On the whole, Roentgen ray pictures conformed well with the clinical findings, but in a few cases no clear Roentgen ray changes were found in cases where clinical signs were unmistakable. All the Roentgen ray readings were made without knowledge of the clinical findings, in order to obtain an independent Roentgen ray judgment uninfluenced by the clinical findings. By comparing the two examinations a final diagnosis was made. The following table gives a survey of our findings:

TABLE 2.—SURVEY OF CLINICAL AND ROENTGEN RAY FINDINGS

Age (mos.)	Clinical diagnosis Rickets			Roentgen ray diagnosis Rickets			Final diagnosis Rickets			Rickets (%)
	+	-	Healed	+	-	Healed	+	-	Healed	
3 . . .	4	3	..	6	1	..	6	1	..	86
4 . . .	3	1	..	3	1	..	4	..	..	100
5 . . .	20	2	..	19	2	1	20	1	1	95
6 . . .	23	5	..	25	2	1	25	3	..	89
7 . . .	32	10	..	34	7	1	33	8	1	81
8 . . .	4	1	..	3	1	1	3	1	1	80
9 . . .	26	16	..	30	11	1	33	7	2	83
10 . . .	16	4	..	15	2	3	15	1	4	95
11 . . .	10	6	..	13	2	1	11	4	1	75
12 . . .	1	..	..	..	1	..	..	..	1	
18 . . .	8	34	..	15	23	4	15	23	4	45
24 . . .	2	8	..	3	5	2	3	5	2	50
Totals . .	149	90	..	166	58	15	168	54	17	
Rickets . .	63%			75%			77%			

The finding of 77% of all children between 3 months and 2 years affected with rickets reveals a considerably higher percentage of rickets than Thoroddsen found. Our clinical examination alone showed a higher percentage of rickets than Thoroddsen found, but she remarked (l.c.) that her figures were rather too low than too high.

*Influence of Cod-liver Oil and Ultraviolet Light.* Information was obtained from the mothers as to whether cod-liver oil had been administered or the child had been exposed to irradiation by ultraviolet light. The following table gives a survey of this enquiry:

TABLE 3.—EFFECT OF COD-LIVER OIL AND ULTRAVIOLET LIGHT

Treatment	Rickets			Free of rickets (%)
	+	—	Healed	
Cod-liver oil . . . . .	99	41	12	34
Ultraviolet irradiation, 7 times or more . . . . .	15	18	6	62
No treatment . . . . .	44	4	0	8

**Comment.** This survey indicates that practically every child will develop rickets in this country unless it receives some kind of prophylactic treatment, either D vitamin in some form or direct irradiation.

In this survey we saw few bones with clear straight calcification lines and distinct spongiosa structure, and such findings were chiefly limited to children who had received artificial sun baths for a longer period. If such bones had been taken as a norm, all the children examined would have been considered rachitic, with very few exceptions.

However, although the question as to what should be looked upon as a norm in growing bones is a debatable one, there can be no doubt that rickets is very prevalent in Iceland, although high degrees of it are rare. M. B. Schmidt<sup>3</sup> has pointed out that rickets may present different aspects in different localities. Here, the disease seems mainly to affect the cranial bones and the ribs, which may show very conspicuous changes although no clinical and even no Roentgen ray changes may be found in the long bones of the extremities.

The occurrence of rickets in spite of cod-liver oil is apparently due to insufficient dosage. Most children receive only 1 teaspoonful a day, containing 2 to 3 gm. of oil which contains 200 to 250 I.U. per gm. or a daily dose of 400 to 750 I.U. This dose is less than half of what is regarded as necessary for the average child (1500 I.U.), although much higher doses may be required in some cases. It is, therefore, not surprising that irradiation gave the best results.

Owing to the long dark winter months in this country, specific anti-rachitic therapy is required during this period, for the long days of summer do not afford adequate protection, no matter how well utilized, against the long and dark winter. Higher doses of cod-liver oil than have been commonly used up to this time are required, and the value of ultraviolet irradiation is being more and more appreciated by the population.

**Summary.** A survey was made on 253 children in Iceland, all between 3 months and 2 years of age. Each child was examined clinically and with Roentgen rays of wrist and knee, usually also including crus and ankle.

The clinical examination showed definite signs of rickets in 66%. Of these, 35% had a visible Harrison's groove, 44% a rachitic rosary, and definite signs of cranial rickets were found in at least 54%. Roentgen ray photographs showed signs of rickets in 75% of the children.

The final result, obtained by comparing clinical and Roentgen ray examination, showed an incidence of 77% with rickets.

These results dismiss the widespread belief that rickets is unknown in Iceland.

#### REFERENCES

1. LINDBLOM, K.: Early Röntgen Signs in Rickets, *Acta path.*, Stockholm, 25, 170, 1939.
2. SCHLEISNER: *Island undersøgt fra et lægevidenskabeligt Synspunkt*, Copenhagen, p. 30, 1849.
3. SCHMIDT, M. B.: Referat über Rachitis und Osteomalacie, *Verh. d. deutsch. Path. Ges.*, 13, 13, 1909.
4. THORODDSEN, K.: Infantil rachitis i Reykjavik, *Læknablaðið*, vol. 9, 1932.
5. WINBERGER, H.: Klinisch-radiologische Diagnostik von Rachitis, *Ergebn. d. inn. Med. u. Kinderheilk.*, 28, 264, 1925.

### HEMORRHAGIC TELANGIECTASIA WITH PULMONARY ARTERY ANEURYSM: CASE REPORT

BY R. WAYNE RUNDLES, PH.D., M.D.

INSTRUCTOR IN INTERNAL MEDICINE, ANN ARBOR, MICH.

(From the Thomas Henry Simpson Memorial Institute, University of Michigan)

HEREDITARY hemorrhagic telangiectasia (Rendu,<sup>21</sup> Osler,<sup>17</sup> Weber<sup>28</sup>) is an uncommon disease characterized by the familial occurrence of anomalous groups of capillary and venous dilatations which are subject to repeated hemorrhage. The following case illustrates many typical aspects of this disease and shows, in addition, some unusual features.

**Case Report.** E. D., No. 389283, a 56 year old factory worker was admitted to the University Hospital on January 17, 1944, complaining of recurrent abdominal pain, weakness, and poor vision. His general health had been good during his earlier life but for 2 years he had been unable to work.

When about 14 years of age, after a fall and slight injury to his nose, he began to have brisk nosebleeds once or twice every week, losing an ounce or more of blood each time. The nosebleeds continued throughout the years, later becoming less profuse but then occurring nearly every day. No other source of bleeding was noted, nor was there excessive bleeding from cuts and scratches.

When about 35 years of age he had for a time recurrent epigastric pain between meals and at night, which was relieved by the ingestion of food and soda. Roentgen examination at a Marine Hospital was reported to reveal a peptic ulcer, and he was treated for 6 weeks with a milk diet and Sippy powders. The symptoms subsided and did not recur.

He was first admitted to the University Hospital on September 15, 1936, 6 weeks after the onset of dull, sometimes colicky, abdominal pain referred to an area about and below the umbilicus. The pain occurred at various times during the day and night without relation to meals, exertion, or other external factors. There was no relief following ingestion of food or alkalies. He had noted no change in bowel habits, but some of his stools were black. Two weeks before admission he became weak and short of breath. With more than slight exertion he had palpitation, dyspnea, and chest pain. Pitting edema of the legs and persistent vomiting developed shortly before his admission to the hospital.

Physical examination showed a well developed and well nourished but very pale white male. About the lips, tongue and the oral mucous membranes there were many small, reddish macules 1 to 3 mm. in diameter. The blood pressure was 155/55 mm. Hg. The thorax was somewhat asymmetrical. The heart was not enlarged and the rate and rhythm were normal. An early systolic murmur was audible at the cardiac apex. The percussion note was resonant over both lung fields and there were no thrills. A continuous murmur, entirely separate from the heart sounds, was heard in a localized area in the 5th intercostal space below and outside the right nipple. The murmur was accentuated late in systole, became very faint during diastole, and was much louder after inspiration. There was pitting edema over the lower legs.

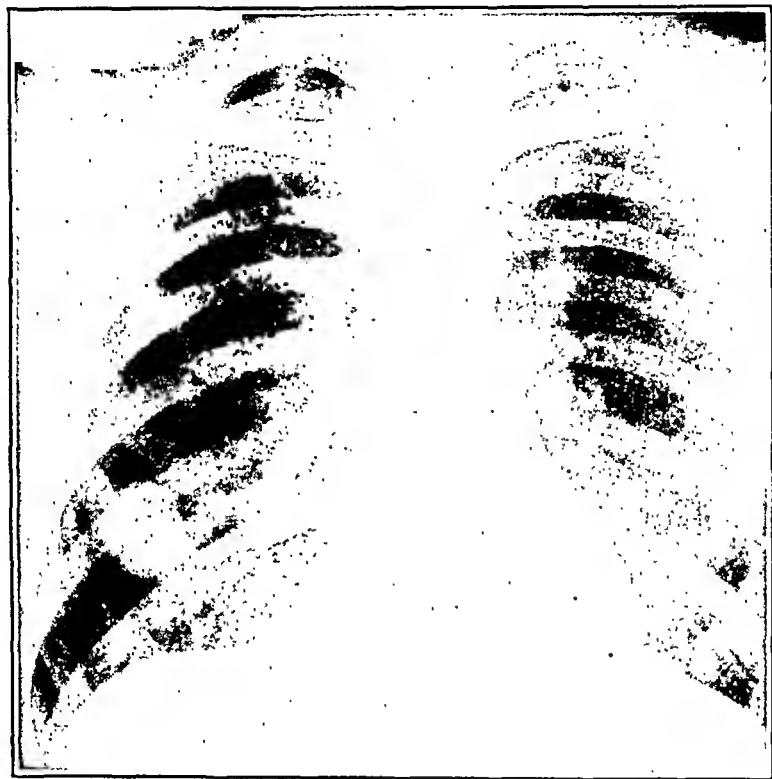


FIG. 1.—Chest roentgenogram on the first admission showing the rounded opacity anteriorly in the right lung and the vascular shadow connecting it with the hilum. A loud murmur was audible over the adjacent chest wall.

Examination of the blood showed a hemoglobin value of 26% (Sahli) and a red cell count of 3,100,000 per c.mm. Urinalysis and several Kahn tests were negative. Gastric analysis revealed no free hydrochloric acid in the gastric contents after subcutaneous injection of histamine. Several stool specimens gave strongly positive guaiac reactions. An electrocardiogram was not definitely abnormal. Sound records from the heart and right chest area confirmed the auscultatory findings but added no further information. A chest roentgenogram showed a sharply circumscribed nearly round, homogeneous opacity about 4 cm. in diameter in the right middle lobe area (Fig. 1). Extending from the opacity to the pulmonary hilum there was a prominent vascular trunk. On fluoroscopy the tumor moved during inspiration and expiration with respect to the chest wall. Slight expansile pulsation was observed fluoroscopically and this was confirmed by kymographic films. Roentgen examination of the gastro-intestinal tract revealed no abnormalities.

The patient received 4 blood transfusions during his hospital stay and ferrous sulfate by mouth. He was discharged after 5 weeks, feeling entirely well.

At home he resumed work and for nearly 5 years considered himself well. Nosebleeding continued as before, nearly every day. In the fall of 1942 there was a recurrence of mid-abdominal pain coming at various times during the day and night without relation to meals and not relieved by food or alkalis. Black stools were noted and he soon became weak, pale, dizzy when standing, and short of breath when active. He was taken to a local hospital where a blood transfusion was given, after which he was discharged with a box of tablets containing iron. He gradually improved during the following months but was never well, being able to work only about one-third of the time at easy jobs. Several months later another identical episode of abdominal pain followed by tarry stools and symptoms of a severe anemia occurred, with slow and incomplete recovery after 2 blood transfusions.

Early in January 1944, 2 weeks before his second hospital admission, the abdominal pain again returned and he soon became pale and too weak to get out of bed. On 1 day there were 3 urgent passages of black, tarry stools. He was taken to a local hospital, given a blood transfusion, and then transferred to the University Hospital for further treatment.

Physical examination on the second hospital admission showed a well-developed male who appeared weak and chronically ill. There were bilateral, mature, senile cataracts. About the lips, tongue and nasal septum there were numerous reddish-blue telangiectasia, 1 to 3 mm. in diameter, very slightly raised above the level of the mucosa. A few similar structures were visible over the forearms and finger-tips. The heart was borderline in size, and at the apex a blowing systolic murmur was audible. Over both lung fields the percussion note was resonant, and fremitus and breath sounds were normal. A moderately loud, continuous murmur, entirely separate from the sounds over the precordium, was audible as before over the right anterior chest, being loudest in an area 3 to 4 cm. in diameter in the 5th intercostal space just outside the mid-clavicular line. The murmur was accentuated in late systole with a faint, low-pitched sound continuing through expiration. The murmur became nearly twice as loud with full inspiration. The tip of the spleen was palpable 2 cm. below the left costal margin at the end of deep inspiration.

Urinalysis and Kahn tests were again negative and the stools gave strongly positive tests for occult blood. The hemoglobin was 30% (4.8 gm.) and the red cell count was 4,500,000 per c.mm. In the stained blood film the red cells appeared extremely pale and varied greatly in size. The mean corpuscular volume was 65  $\mu$ .

A chest roentgenogram showed the previously described opacity in the right lung field and the prominent vascular shadow connecting it with the pulmonary hilum. There had been no more than a slight increase in size during the previous 7 years. On fluoroscopy the tumor appeared to change slightly in shape during respiration and to become denser during inspiration. There were no other definite abnormalities in either lung, although 2 small somewhat variable shadows were present that were difficult to interpret. Roentgen examination of the gastro-intestinal tract was negative.

A gastroscopic examination (Dr. H. M. Pollard) provided a satisfactory view of the interior of the stomach up to and including the pyloric valve. The mucosa was definitely pale. Several clusters of telangiectasia were visible along the lesser curvature and on the anterior wall, and a few were present in the antrum and one on the pyloric valve. Each telangiectasis was circular, 2 to 3 mm. in diameter, sharply circumscribed, and intensely red. The dilated vessels were level with the surface of the mucosa and did not protrude into the lumen. Fresh blood oozed from the gastric mucosa in 2 or 3 areas.

A sigmoidoscopy was performed and no telangiectasia were seen.

The patient was given ferrous sulfate 0.6 gm. 3 times daily. After 1 week the red cell count had risen to 5,000,000, the hemoglobin to 57% (8.9 gm.) and the mean corpuscular volume to 70  $\mu$ . At the end of 2 weeks the red cell

count was 5,200,000, the hemoglobin 69% (10.7 gm.), and the mean corpuscular volume 79  $\mu$ . An uneventful cataract extraction was then carried out.

When discharged home he was advised to supplement his daily diet with ferrous sulfate permanently. On a check-up examination 3 months later he reported that his general health was vastly improved. He had had an occasional episode of abdominal pain but no tarry stools. One nosebleed had been profuse and had lasted 5 days. Physical examination showed nothing new except greatly improved general health. The R.B.C. count had increased to 5,700,000, the hemoglobin to 109% (17.1 gm.) and the average cell volume to 95  $\mu$ . A second cataract operation was performed without complication.

The patient's parents were over 80 years of age, living and well. He was one of 8 children, and had 1 daughter and 1 granddaughter. None of his relatives were known to have had frequent epistaxes or other types of abnormal bleeding, nor to have had visible telangiectasia. None of his family were available for examination.

The general clinical features of hereditary hemorrhagic telangiectasia have been presented in many publications.<sup>1,4,10,12,14-16,18,19,25-27</sup> The hereditary nature of the malady has been of most general interest. The sexes are equally affected, and both males and females may transmit the disease to their offspring. In many families the disease appears to be inherited as a dominant characteristic but several instances of skipped generations in afflicted families have been recorded (Osler,<sup>17</sup> Weber,<sup>28</sup> Steiner,<sup>25</sup> Audry,<sup>2</sup> Fitz-Hugh,<sup>6</sup> Foggie,<sup>8</sup> Edel, Van Gilse and Postma,<sup>4</sup> Hurst and Plummer,<sup>13</sup> and Singer and Wolfson<sup>24</sup>). It is believed that this "atavistic" or recessive hereditary transmission may account for the many otherwise typical cases, such as the one reported here, in which no positive family history can be obtained.<sup>9</sup>

Epistaxis is the commonest symptom, since delicate, easily traumatized telangiectasia occur most frequently on the nasal septum, but bleeding from the skin or oral mucous membranes occurs in the majority of patients and may even be the exclusive site of hemorrhage. The telangiectasia usually do not appear before the age of puberty. In the 3rd and 4th decades of life they become more numerous and more subject to hemorrhage. The individual groups of dilated vessels are not entirely permanent structures but tend to vary from time to time in number, in size, and in tendency to bleed. An anemia severe enough to be incapacitating often results from the long-continued blood loss, and a number of fatal hemorrhages have been reported.

The frequency of internal bleeding in patients with hereditary hemorrhagic telangiectasia has been emphasized by several recent authors. Hematemeses, hemoptyses, melena, hematuria, and even cerebrovascular accidents have many times been attributed to bleeding from telangiectasia, although clinical or pathologic proof has been infrequent. One of Osler's<sup>17</sup> patients died of carcinoma of the stomach, and necropsy disclosed the presence of many gastric telangiectasia. Boston<sup>3</sup> reported 3 patients with hemorrhagic telangiectasia who had had repeated attacks of gastric hemorrhage. Surgical exploration was necessary to control hemorrhage in one of his patients and gastric bleeding from a small cluster of abnormal vessels was found. One of Fitz-Hugh's<sup>7</sup> patients had had hemoptyses, and bronchoscopy revealed distinct telangiectasia which bled with the slightest pressure in the trachea and in the left bronchus. Telangiectasia were also seen in the

lower colon by sigmoidoscopy and their histologic nature was confirmed by biopsy. Four years later, however, at autopsy there were no telangiectasia visible in either the respiratory passages or in the gastrointestinal tract. Hurst and Plummer,<sup>13</sup> also, emphasized gastro-intestinal hemorrhage as a complication of this disease. In 3 typical cases, and in 1 in which there was no confirmatory family history, telangiectasia were seen by sigmoidoscopy. Renshaw<sup>22</sup> was the first to see hemorrhagic telangiectasia in the stomach by gastroscopy and gave an excellent description of their appearance. His patient had had episodes of severe gastro-intestinal bleeding for 12 years with recurrent severe anemia. Roentgen examination of the stomach and colon was negative and telangiectasia were not seen by sigmoidoscopic examination. No family history of the disease was mentioned. Griggs and Baker<sup>11</sup> reported 3 patients with hereditary hemorrhagic telangiectasia whose presenting complaints were gastro-intestinal bleeding. The exact origin of the bleeding was not discovered, since roentgen examination was negative in all cases and in the one patient in whom gastroscopic and sigmoidoscopic examination were done no telangiectasia were seen. All of their patients, as the one in the present report had abdominal distress which recurred during the periods of active bleeding.

Detailed pathologic studies in hereditary hemorrhagic telangiectasia have been very few. The 9 published necropsy reports were recently reviewed by Schuster<sup>21</sup> in reference to the multiple vascular abnormalities which occurred in a typical case in which he performed a complete postmortem examination. Telangiectasia in his case were present in the skin, nose, mouth, pharynx, larynx, trachea, stomach and duodenum. None were present in the bronchi, colon, rectum, kidneys, or serous membranes. Dilated and distorted fibrotic veins were present in the upper lobe of one lung and beneath the surface of the liver capsule. A unique feature was the presence of multiple aneurysms of the splenic artery each about the size of a hazel-nut. The relation of these vascular anomalies to the capillary and venous dilations which characterize this disease is still uncertain.

Aneurysm of the pulmonary artery has not been reported previously in any patient with hereditary hemorrhagic telangiectasia. The roentgen appearance and physical findings in our case strongly suggest an arterial dilatation comparable to the splenic aneurysms described by Schuster, although a vascular tumor with arteriovenous communication might possibly account for the findings. Thoracotomy and lobectomy was considered at the time of the first admission of our patient. The almost complete stability of the lesion for over a period of 7 years indicated a better prognosis than was first suspected and operation was finally considered inadvisable.

The treatment of hereditary hemorrhagic telangiectasia is difficult and somewhat unsatisfactory. Trauma, a factor of importance in the development of the telangiectasia<sup>12</sup> as well as in inducing bleeding from them, can be avoided to some degree with respect to exposed surfaces. Iron is the only medication of proved value, and in those subject to chronic blood loss it should be used continuously. The local treat-

ment of nasal telangiectasia with chromic acid,<sup>12</sup> radium, or electro-desiccation<sup>5</sup> has been of definite benefit in some patients in the control of epistaxis. An inflated finger cot has long been recommended as the most effective method of controlling profuse nasal hemorrhage.<sup>17</sup> No satisfactory method of dealing with internal hemorrhage other than treatment of the anemia and use of blood transfusions when necessary has been devised.

**Summary.** A case is reported of a patient with hemorrhagic telangiectasia who had suffered from repeated epistaxis from the age of 14, and in later life from gastro-intestinal hemorrhage severe enough to produce a severe, incapacitating anemia. Multiple gastric telangiectasia were seen by gastroscopic examination. An aneurysm of the pulmonary artery was present which did not increase appreciably in size during a period of over 7 years observation.

#### REFERENCES

1. AUBERTIN, CH., LEVY, ROBERT, and BACLESSE, M.: *Presse méd.*, 41, 185, 1933.
2. AUDRY: Reference by Fitz-Hugh.<sup>6</sup>
3. BOSTON, L. N.: *AM. J. MED. SCI.*, 180, 798, 1930.
4. EDEL, K., VAN GILSE, P. H. G., and POSTMA, C.: *Acta oto-laryng.*, 13, 524, 1929.
5. FIGI, FREDERICK A., and WATKINS, CHARLES H.: *Ann. Otol., Rhinol. and Laryngol.*, 52, 330, 1943.
6. FITZ-HUGH, THOMAS: *AM. J. MED. SCI.*, 166, 885, 1923.
7. FITZ-HUGH, THOMAS: *AM. J. MED. SCI.*, 181, 261, 1931.
8. FOGGIE, W. E.: *Edinburgh Med. J.*, 35, 281, 1928.
9. GOLDSTEIN, HYMAN I.: *Arch. Int. Med.*, 48, 836, 1931.
10. GJESSING, E.: *Derm. Ztschr.*, 23, 193, 1916.
11. GRIGGS, DONALD E., and BAKER, MARSHALL Q.: *Am. J. Dig. Dis.*, 8, 344, 1941.
12. HANES, FREDERIC M.: *Bull. Johns Hopkins Hosp.*, 20, 63, 1909.
13. HURST, A. F., and PLUMMER, N. S.: *Guy's Hosp. Rep.*, 82, 81, 1932.
14. HUTCHISON, ROBERT, and OLIVER, W. J.: *Quart. J. Med.*, 9, 67, 1916.
15. KELLY, A. BROWN: *Glasgow Med. J.*, 65, 411, 1906.
16. LARRABEE, RALPH C., and LITTMAN, DAVID: *New Eng. J. Med.*, 207, 1177, 1932.
17. OSLER, WILLIAM: *Bull. Johns Hopkins Hosp.*, 12, 333, 1901.
18. OSLER, WILLIAM: *Quart. J. Med.*, 1, 53, 1907.
19. PAUL, S. NORMAN: *Brit. J. Derm.*, 30, 27, 1918.
20. REINIGER, A.: *Wien. med. Wehnschr.*, 81, 1590 and 1681, 1931.
21. RENDU, M.: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 3, 731, 1896.
22. RENSHAW, JOHN F.: *Cleveland Clin. Quart.*, 6, 226, 1939.
23. SCHUSTER, NORAH H.: *J. Path. and Bact.*, 44, 29, 1937.
24. SINGER, KARL, and WOLFSON, WILLIAM Q.: *New Eng. J. Med.*, 230, 637, 1944.
25. STEINER, WALTER R.: *Arch. Int. Med.*, 19, 194, 1917.
26. ULLMAN, KARL: *Urol. and Cut. Rev.*, 37, 619, 1933.
27. VAN BOGAERT, LUDO, and SCHERER, J. H.: *Ann. de méd.*, 38, 291, 1935.
28. WEBER, F. PARKES: *Lancet*, 2, 160, 1907.

#### TISELIUS ELECTROPHORESIS STUDIES OF PLASMA PROTEINS IN ADDISON'S DISEASE

BY E. PERRY McCULLAGH, M.D.

AND

L. A. LEWIS, PH.D.

CLEVELAND, OHIO

With the technical assistance of JAMES CLARK, A.B.

(From the Cleveland Clinic)

THE importance of the adrenal cortex in maintaining normal plasma composition is well established. Several crystalline preparations,



notably desoxycorticosterone acetate and corticosterone, are capable of maintaining a normal plasma electrolyte concentration and blood volume in the adrenalectomized animal and the patient with Addison's disease. Levin and Leatham,<sup>2</sup> and Hartman *et al.*<sup>1</sup>, reported plasma protein studies in adrenalectomized animals. They found a lowered albumin level in the plasma of dogs and cats. In experiments reported by Hartman *et al.*<sup>1</sup> the low albumin-globulin ratio was found to persist whether the adrenalectomized animal was maintained on whole adrenal extract, desoxycorticosterone acetate, sodium salts, Hartman's "sodium factor," or "cortin."

The plasma protein fractionations mentioned were determined by the "salting out" method, which is open to considerable error. The present studies were carried out using the Tiselius electrophoresis method, which provides a more accurate and complete fractionation of the various plasma proteins.

**Subjects, Materials and Methods.** Nineteen patients with proved Addison's disease were studied. The diagnosis was established by physical examination and confirmed by pertinent laboratory findings such as low serum sodium, high serum potassium, low indices with the Robinson-Power-Kepler test, and hemoconcentration. Of these patients, 6 were followed over a period of months to determine what changes occurred in the plasma protein picture during adrenal insufficiency and after various types of replacement therapy.

The Tiselius electrophoresis technique as modified by Longsworth was used.<sup>5</sup> Total and non-protein nitrogen were determined by the Pregl modification of the micro-Kjeldahl method.<sup>6</sup> A detailed description of methods used in this laboratory has been published.<sup>3</sup>

Desoxycorticosterone acetate, administered either in an oil base or in pellets, whole beef adrenal extract, and pig adrenal extract were the materials used in treatment. Beef adrenal extract in an aqueous base was administered intramuscularly usually twice daily. Hog adrenal extract in an oil base was injected intramuscularly once daily. Pellets of desoxycorticosterone acetate were implanted subcutaneously. Replacement of pellets was usually required in 9 to 12 months.

**Results.** The results of studies made when definite signs of adrenal insufficiency were present are summarized in Table 1. In 4 of the 7 cases the total plasma protein fell in the upper normal range. Hemoconcentration was present. It is evident that this makes the plasma protein levels appear higher than they would be if the plasma volume had been normal. It also means that since hemodilution takes place during therapy the increase in the total circulating plasma protein is greater than would be indicated by the plasma protein concentration level alone, and the amount of albumin necessary to bring the concentration to normal levels is greater than would be indicated if plasma volume is not considered. In 1 case the total protein was very low, being 4.54 gm. per 100 ml. This patient was extremely emaciated, which probably accounted for the severity of the protein depletion. In all studies the percentage of albumin was low, and in 5 cases the total protein in gm. per 100 ml. was below normal limits. There was no consistent increase in any globulin fraction.

Table 2 summarizes the data obtained on 5 of these patients after months of therapy, and on 4 others repeatedly studied, Cases 1 to 4

showed a definite increase in the percentage of albumin after amelioration of symptoms of adrenal insufficiency and during good maintenance.\* In no case was the albumin restored to normal levels when the patient was maintained on desoxycorticosterone acetate alone or with small supplementary amounts of adrenal extract. When Case 5 received 15 ml. of adrenal extract in divided doses each day for 4 weeks, the protein distribution became entirely normal. When the extract was changed to hog adrenal extract for 3 weeks, the normal distribution was maintained. Case 7 also showed some increase in the percentage of albumin over that attained with desoxycorticosterone acetate when adrenal extract was used for a long time. The normal level, however, was never attained. Treatment with hog adrenal extract had no beneficial effect; the albumin percentage after 13 weeks closely approximated that observed when the patient received desoxycorticosterone acetate.

Case 6 may possibly have shown a slight increase in albumin percentage when receiving hog adrenal extract. Cases 8 and 9 showed no further improvement in the plasma albumin level when adrenal extract was added to the treatment.

Table 3 summarizes the data on the remaining 9 cases. Case 12 was especially interesting, since the patient appeared to have absolutely complete replacement as judged by physical reactions and sense of well-being when maintained on desoxycorticosterone acetate. He was the only one who had an entirely normal protein distribution when receiving desoxycorticosterone acetate alone. Case 12 was also especially well maintained by desoxycorticosterone acetate, and the protein distribution was nearly normal.

**Discussion.** It is altogether possible that insufficient dosage was responsible for the failure of the plasma protein picture to be restored to normal in some patients treated with adrenal extract. On the other hand, they appeared to be well maintained clinically. It is possible that the factors essential for maintenance of normal protein distribution were not present in sufficient amounts, while principles physiologically active in other ways, factors regulating salt and water balance or carbohydrate metabolism, were administered in adequate quantities.

In Case 2 lack of any immediate alteration in protein distribution during treatment with very large amounts of adrenal extract would indicate that, at least in the patient with Addison's disease, no stores of albumin are readily available to be brought forth after hormone injection, or that albumin and globulin stores are released at such a rate that the distribution is unaltered. The latter assumption seems rather unlikely. Between the first two studies in Case 2 the volume of circulating plasma increased by 12.5% as judged by the decreased hematocrit value, and the plasma protein concentration fell 20%. Estimation of modifications in circulating plasma volume based on

\* Maintenance of a normal serum electrolyte level, an essentially normal blood pressure, absence of edema or puffiness and nausea, a good appetite, normal or almost normal energy and endurance and a sense of well-being.

TABLE 1.—TISELIUS PROTEIN DISTRIBUTION IN ADRENAL INSUFFICIENCY

Case No.	Treatment	Degree of insufficiency	ADRENAL INSUFFICIENCY															Blood pressure
			Albumin			$\alpha$ -globulin			$\beta$ -globulin			$\gamma$ -globulin			Fibrinogen			
		Average range	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein		
1	None		6.51	4.09	62.7	0.47	7.2	0.81	13.1	0.77	11.7	0.33	5.4		86/72			
2	None		5.94		60.1	0.39	6.0	0.65	11.0	0.60	8.0	0.16	2.8		110/70			
3	5 ml. adrenal extn. per day, 2 weeks	Extreme	7.82	5.11	67.2	0.66	8.7	1.07	15.9	0.91	14.8	0.48	7.2		90/50			
4	1 2 ml. adrenal extn. per day, 4 days	Moderate	7.04	3.29	46.8	0.72	10.2	1.02	14.5	1.39	19.7	0.65	8.8		86/72			
5	None	Mild	6.08	3.26	47.8	0.82	12.0	1.13	16.5	0.78	11.5	0.83	12.2		110/70			
6	None	Extreme	5.98	2.66	43.6	0.81	13.4	0.93	15.3	1.03	17.0	0.65	10.7		90/50			
7	None	Moderate	7.21	3.30	55.1	0.39	0.5	0.67	11.2	1.66	17.9	0.56	9.3		96/68			
		Extreme	7.22	4.01	55.6	0.46	6.4	1.01	14.4	1.21	10.7	0.49	6.9		80/56			
			4.54	2.39	52.2	0.45	0.1	2.00	27.8	0.57	7.9	0.45	6.2		90/60			
					52.7	0.43	9.1	0.72	15.8	0.53	11.7	0.47	10.4		70/35			

ADRENAL INSUFFICIENCY			ADRENAL INSUFFICIENCY															Blood pressure
ADRENAL INSUFFICIENCY			Albumin			$\alpha$ -globulin			$\beta$ -globulin			$\gamma$ -globulin			Fibrinogen			
		Average range	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein		
1	None		6.51	4.09	62.7	0.47	7.2	0.81	13.1	0.77	11.7	0.33	5.4		86/72			
2	None		5.94		60.1	0.39	6.0	0.65	11.0	0.60	8.0	0.16	2.8		110/70			
3	5 ml. adrenal extn. per day, 2 weeks	Extreme	7.82	5.11	67.2	0.66	8.7	1.07	15.9	0.91	14.8	0.48	7.2		90/50			
4	1 2 ml. adrenal extn. per day, 4 days	Moderate	7.04	3.29	46.8	0.72	10.2	1.02	14.5	1.39	19.7	0.65	8.8		86/72			
5	None	Mild	6.08	3.26	47.8	0.82	12.0	1.13	16.5	0.78	11.5	0.83	12.2		110/70			
6	None	Extreme	5.98	2.66	43.6	0.81	13.4	0.93	15.3	1.03	17.0	0.65	10.7		90/50			
7	None	Moderate	7.21	3.30	55.1	0.39	0.5	0.67	11.2	1.66	17.9	0.56	9.3		96/68			
		Extreme	7.22	4.01	55.6	0.46	6.4	1.01	14.4	1.21	10.7	0.49	6.9		80/56			
			4.54	2.39	52.2	0.45	0.1	2.00	27.8	0.57	7.9	0.45	6.2		90/60			
					52.7	0.43	9.1	0.72	15.8	0.53	11.7	0.47	10.4		70/35			

TABLE 2.—EFFECT ON TISELIUS PLASMA PROTEIN DISTRIBUTION OF ADDISON'S PATIENTS OF VARIOUS TYPES OF REPLACEMENT THERAPY.

DISTRIBUTION OF ADDISON'S PATIENTS OF VARIOUS TYPES OF REPLACEMENT THERAPY.																		
Case No.	Treatment	Period treated (wks.)	Total protein (gm./100 ml.)	Albumin		$\alpha$ -globulin		$\beta$ -globulin		$\gamma$ -globulin		Fibrinogen		Blood pressure				
				Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein					
1	None																	
	Desoxycorticosterone acetate (pellets 1 wk.)	6	7.04	3.29	46.8	0.72	10.2	1.02	14.5	1.39	19.7	0.05	8.8	80/50				
2	Desoxycorticosterone acetate pellets	32	6.31	3.50	55.6	0.56	8.8	0.91	14.4	1.62	16.1	0.32	5.1	90/60				
	270 ml. adrenal extract, 19 mg. desoxycorticosterone acetate	1	6.69	3.50	57.4	0.44	7.3	0.68	11.2	0.98	16.0	0.49	8.1	90/60				
*	5 ml. adrenal extract, 2.5 mg. desoxycorticosterone acetate per day	1	6.82	3.20	47.8	0.82	12.0	1.13	16.5	0.78	11.5	0.83	12.2	110/80				
3†	5 ml. adrenal extract, 2.5 mg. desoxycorticosterone acetate per day	6	5.42	2.50	46.1	0.86	15.8	0.87	16.1	0.55	10.2	0.64	11.3	110/70				
	Desoxycorticosterone acetate pellets	2	5.34	2.89	52.2	0.64	11.5	0.85	14.8	0.91	15.7	0.67	11.6	80/74				
	Desoxycorticosterone acetate pellets	36	6.08	2.66	43.6	0.81	13.4	0.93	15.3	1.03	17.0	0.65	10.7	124/80				
4	1-2 ml. adrenal extract, 6 mg. desoxycorticosterone acetate per day	38	6.02	3.17	52.7	0.63	10.5	0.85	14.1	0.95	15.7	0.42	7.0	96/50				
	Desoxycorticosterone acetate pellets	4	6.17	3.35	54.3	0.71	11.5	0.86	14.0	0.88	14.2	0.37	6.0	105/70				
5	Desoxycorticosterone acetate pellets	13	5.98	3.30	55.1	0.39	6.5	0.67	11.2	1.06	17.9	0.56	9.3	107/70				
	Desoxycorticosterone acetate, dosage varied	12	6.08	3.55	58.1	0.37	6.1	0.73	12.0	0.82	13.1	0.63	10.4	96/68				
	Desoxycorticosterone acetate, 7.5 ml. adrenal extract, per day	4	7.21	4.01	55.6	0.46	6.4	1.04	14.1	1.21	16.7	0.49	6.9	122/80				
	7.5 ml. adrenal extract, per day	4	7.03	4.07	58.0	0.41	6.2	1.22	17.1	1.30	18.4	..	..	80/56				
	2 ml. hog extr. twice a day	4	6.64	3.78	50.9	0.45	0.7	0.82	12.4	1.14	17.3	0.45	0.7	118/70				
6	Desoxycorticosterone acetate pellets	4	6.50	4.03	61.9	0.44	0.8	0.92	14.2	0.84	12.9	0.27	4.2	134/80				
7	Desoxycorticosterone acetate pellets	3	7.10	4.20	60.0	0.44	6.2	0.91	12.9	0.97	13.6	0.52	7.3	110/76				
8	Desoxycorticosterone acetate pellets	8	6.18	3.37	54.0	0.40	6.4	1.07	17.3	0.81	13.2	0.53	8.5	124/80				
9	Desoxycorticosterone acetate pellets, 7.5 ml. adrenal extract, per day	4	5.97	3.27	54.8	0.38	0.3	0.99	16.6	0.75	12.5	0.68	9.8	115/80				
10	Desoxycorticosterone acetate pellets	12	3.27	54.8	0.38	0.3	0.99	16.6	0.75	12.5	0.68	9.8	9.8	138/90				
11	1.5 ml. hog extr. per day	4	0.42	3.52	54.7	0.43	6.7	0.90	14.1	1.09	17.0	0.48	7.5	132/80				
12	4	Good maint.	6.30	3.64	57.0	0.31	4.8	6.1	15.0	1.20	18.8	0.28	4.4	140/100				
13														140/92				

Case No.	Treatment	Period treated (wks.)	Maintenance	Total protein (gm./100 ml.)	Albumin		$\alpha$ -globulin		$\beta$ -globulin		$\gamma$ -globulin		Fibrinogen		Blood pressure
					Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	
7	Desoxycorticosterone acetate pellets	52	Good maint.	5.67	2.84	50.1	0.39	6.8	1.90	17.6	0.98	17.3	0.46	8.2	118/82
	Desoxycorticosterone acetate pellets, 7.5 ml. adrenal extr. per day	4	Good maint.	6.05	3.06	50.6	0.39	6.4	1.07	17.6	1.21	20.0	0.32	5.4	134/80
	Desoxycorticosterone acetate pellets, 4 ml. adrenal extr. every other day	52	Good maint.	6.62	3.60	54.2	0.48	7.3	1.03	15.6	1.07	16.2	0.44	6.7	120/82
**	1 ml. hog extr., 2 mg. desoxycorticosterone acetate per day	4	Overtreatment	6.24	3.35	53.6	0.48	7.8	0.96	15.4	1.01	16.2	0.44	7.0	105/72
††	1 ml. hog extr., 2 mg. desoxycorticosterone acetate per day	9	Overtreatment	6.71	3.44	51.1	0.42	6.3	1.15	17.1	1.21	18.2	0.49	7.3	102/70
8††	Desoxycorticosterone acetate pellets	31	Fair maint.	6.37	3.29	51.6	0.54	8.5	0.91	14.3	0.91	14.3	0.67	10.5	155/100
§§	Desoxycorticosterone acetate pellets, 5 ml. adrenal extr. per day	4	Good maint.	6.24	3.12	50.0	0.43	6.9	1.06	17.0	1.06	17.0	0.57	9.1	140/90
9	Desoxycorticosterone acetate pellets, nearly exhausted in 46 weeks	46	Slight insuffi.	6.28	3.45	55.0	0.43	6.8	0.71	11.3	1.19	18.9	0.50	8.0	98/70
	1 ml. hog extr. per day, containing 2 mg. desoxycorticosterone acetate	8	Excellent maint.	6.02	3.40	56.5	0.34	5.7	0.72	11.9	1.20	19.9	0.36	6.0	145/96

\* Intermittent nausea.

† Pulmonary tuberculosis, probably arrested.

‡ Serum.

§ Appetite "keen."

\*\* Face and eyelids puffy.

†† 90 gm. protein per day, 5 weeks.

‡ Weakness, headaches.

§§ Intermittent headaches, weakness decreased

TABLE 3.—TISELIUS PLASMA PROTEIN DISTRIBUTION IN TREATED ADDISON'S PATIENTS.

Case No.	Treatment	Period treated (wks.)	Maintenance	Total protein (gm./100 ml.)	Albumin		$\alpha$ -globulin		$\beta$ -globulin		$\gamma$ -globulin		Fibrinogen		Blood pressure
					Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	Gm./100 ml.	% total protein	
11	Desoxycorticosterone acetate pellets	190	Very good maint.	5.80	3.43	59.2	0.49	8.5	0.79	13.6	0.64	11.0	0.45	7.7	105/75
12	Desoxycorticosterone acetate pellets	104	Excellent maint.	6.16	3.74	60.6	0.44	7.1	0.89	14.6	0.80	13.0	0.29	4.7	124/82
13	Desoxycorticosterone acetate pellets	85	Good maint.	6.54	3.67	56.1	0.37	5.7	1.10	16.8	1.06	16.2	0.34	5.2	100/70
14	Desoxycorticosterone acetate pellets	16	Good maint.	6.80	2.74	40.3	1.10	16.2	0.78	11.4	1.34	19.7	0.84	12.4	96/50
15*	1 ml. hog adrenal extr. containing 2 mg. desoxycorticosterone acetate daily	3	Good maint.	6.47	3.35	51.8	0.43	6.7	1.20	18.5	0.96	14.8	0.53	8.2	106/72
16	2.5 mg. desoxycorticosterone acetate, 5 ml. adrenal extr. per day	12	Good maint.	5.37	3.11	57.8	0.43	8.1	0.70	13.1	0.78	14.5	0.35	6.5	118/70
17	2 ml. adrenal extr. per day	6	Good maint.	6.03	3.08	51.0	0.45	7.4	0.78	12.9	1.07	17.9	0.65	10.8	106/80
18†	5 mg. desoxycorticosterone acetate per day	1	Sl. overtreated	5.53	2.65	47.8	0.58	10.5	0.93	16.8	0.91	16.1	0.46	8.3	100/66
19	85 ml. adrenal extract, 18 mg. desoxycorticosterone acetate in 6 days after extreme insuffi.	1	Improvement	4.57	2.26	49.5	0.51	11.2	0.88	19.2	0.49	10.7	0.43	9.4	80/60

\* Complicated by severe muscular contractions especially of knees and elbows.

† Slight edema.

hematoerit determinations only is not entirely valid, but it is believed that during recovery from adrenal insufficiency a good estimate of changes in plasma volume in an individual is probably obtained. Studies on adrenalectomized animals indicated the validity of this conclusion. In adrenalectomized dogs in which the dye method of estimating plasma volume was employed, "the importance of the change in plasma volume in modifying the red blood cell count and hemoglobin value is clearly shown by the blood volume decrease."<sup>4</sup> By frequent injections of adrenal extract and administration of desoxycorticosterone acetate in oil a constant supply of hormone was assured the patient at all times.

**Summary.** In the estimation of plasma proteins in 19 patients with Addison's disease, the Tiselius electrophoresis method was used for determination of the various protein fractions. When the patient showed definite signs of adrenal insufficiency, the total protein was usually in the upper normal range, and in all cases the albumin percentage of the total protein was definitely decreased. The increase in globulin was not consistent in any one fraction or fractions. All globulin fractions usually showed some increase.

After adequate maintenance with desoxycorticosterone acetate for a period of months, the albumin increased somewhat but did not return to normal. When large amounts of adrenal extract were used for a month or longer, further improvement was observed, and in some instances a normal or nearly normal protein distribution was attained.

We are greatly indebted to Dr. G. F. Cartland and Dr. Dwight Ingle of the Upjohn Company and Dr. David Klein of the Wilson Company for the adrenal extract used in these studies.

#### REFERENCES

1. HARTMAN, F. A., LEWIS, L. A., THATCHER, J. S., and STREET, H. R.: Effect of Adrenal Factors on Plasma Proteins, *Endocrinology*, 31, 287, 1942.
2. LEVIN, L., LEATHEM, J. H., and CRAFTS, R. C.: The Effects of Adrenalectomy and Replacement Therapy on the Serum Protein Levels of the Cat, *Am. J. Physiol.*, 136, 776, 1942.
3. LEWIS, L. A., and McCULLAGH, E. P.: Electrophoretic Analysis of Plasma Proteins in Hyperthyroidism and Hypothyroidism, *Am. J. Med. Sci.*, 208, 727, 1944.
4. LEWIS, L. A.: The Blood Picture of Adrenalectomized Animals Treated With Different Adrenal Fractions, *Endocrinology*, 28, 821, 1941.
5. LONGSWORTH, L. G.: A Modification of the Schlieren Method for Use in Electrophoretic Analysis, *J. Am. Chem. Soc.*, 61, 529, 1939.
6. PREGL, F.: *Quantitative Organic Micro-analysis*, 2nd Engl. ed., Philadelphia, Blakiston, 1930.

## THE INCIDENCE, CAUSES AND INTERMITTENCY OF PROTEINURIA IN YOUNG MEN

By IRVING J. WOLMAN, M.D.

SURGEON (R), U. S. PUBLIC HEALTH SERVICE  
SHEEPSHEAD BAY, BROOKLYN 29, N. Y.

(From the U. S. Maritime Service Training Station and the U. S. Public Health Service Hospital)

THIS paper reports a study of proteinuria in men being mobilized for war service, designed to answer certain questions: (1) What evidence lies behind the modern view that in the absence of associated

disturbances intermittent proteinuria of young persons is inconsequential and benign? (2) What is the incidence and nature of proteinuria in American men of supposed good health? (3) Does measurement of the concentration of protein assist in tracing the etiology of the proteinuria? (4) How effective is one urine analysis for recognizing and differentiating between nephritis, urologic disease and intermittent proteinuria?

Although by special methods trace amounts of mucins can be demonstrated in every normal or "negative" urine,<sup>31,39</sup> the tests for proteinuria as ordinarily performed detect albumins and globulins only.<sup>6</sup> In clinical proteinuria the proteins are identical in physical and immunologic properties with those of the blood,<sup>3,7,14,27</sup> but not the same nor as uniform in fractional distribution. When present, such urine proteins are referred to by tradition as "albumin," yet globulins are almost always present also, especially in nephritis and nephrosis. The term "proteinuria" is more exact and is to be preferred.

**The Benign Nature of Intermittent Proteinuria.** From the standpoint of the urine analysis itself, apart from clinical history and physical examination, intermittent or *orthostatic* proteinuria differs from nephritic proteinuria in two fundamental respects. Firstly with all varieties of nephritis—acute or chronic, glomerular, arteriosclerotic or pyelonephritic—the excretion of protein is almost always constant, regardless of posture or exercise.<sup>18,21</sup> The sole exceptions to this rule seem to be those occasional patients with mild chronic glomerulonephritis which remains subclinical and asymptomatic for years, and those convalescent from acute nephritis, when nearly well. In such types of cases the proteinuria may be absent or very slight when the individual is resting, but usually reappears during physical activity or on assumption of the lordotic position. Sometimes, too, a momentary clearing of a mild nephritic proteinuria can be effected during the forcing of fluids or by feeding alkali in large doses.<sup>6,9,35</sup> Secondly, nephritis invariably gives rise to erythrocytes and casts in the urinary sediment<sup>6</sup>; without this finding the diagnosis cannot be made. Even the exceptional mild or latent patients in whom the proteinuria is no longer constant usually excrete an increased number of red cells and casts, detectable by careful microscopy of fresh specimens or by quantitative procedures such as the Addis sediment count.<sup>1</sup> Thus, intermittent proteinuria (referring to the disorder, not the mere finding) is viewed by definition and custom as a urinary dysfunction distinct from true nephritis.

At times it is not easy to differentiate between the pure form of intermittent proteinuria and that which occurs in association with urologic disorders. It was noted in the series of trainees discussed later in this paper that proteinuria of extrarenal origin when present at all was more often discontinuous than regular. Rytand<sup>37</sup> has described 2 patients with urinary anomalies, who had clear negative urine when lying down, but on standing showed proteinuria associated with impaired diodrast excretion and the outpouring of casts, erythrocytes and renal epithelial cells. Young *et al.*,<sup>41</sup> and Prince<sup>36</sup> have advised an

exhaustive investigation of every patient with proteinuria, to include along with the history and urine studies, the establishment of "normal kidney function (phthalein, urea clearance and dilution and concentration tests); normal blood chemistry, non-protein nitrogen, blood urea, total protein and albumin-globulin ratio; and negative plain Roentgen rays and normal intravenous urograms." However, the wide prevalence of proteinuria makes the practical carrying out of such a detailed diagnostic program economically unfeasible.

*One major reason for holding intermittent uncomplicated proteinuria to be benign* is its high rate of occurrence in groups of individuals otherwise normal, as compared with the relative rarity of kidney diseases in the same populations. Thus MacLean,<sup>29</sup> during the first World War on studying 50,000 British soldiers with salicylic acid reagent, found that 5.6% had proteinuria, in a single test. After deduction of specimens containing pus or spermatozoa and those with "less than 5 mg. per 100 cc." the more significant figure of 2.2% was secured.

Of 7041 French and British troops examined by McLeod and Ameuille,<sup>30</sup> in 1916, for proteinuria with the single specimen method, 263 positives (3.7%) were encountered.

Of 2269 cadets and officers at West Point Military Academy studied by Ashburn,<sup>2</sup> between 1925 through 1927, 360 (almost 16%) had proteinuria (quantities not stated), two-thirds of the cases being encountered in a single year. Of these, proteinuria was present once in 80%, twice in 16%, and more than twice in but 4%. Among 64 cadets showing protein at more than one examination, in 10 instances positive results were separated by a negative one. In 1 cadet the condition continued for 4 years and then cleared.

The incidence in 20,000 freshmen at the University of Minnesota, using the nitric acid ring test, was studied by Diehl and McKinlay;<sup>18</sup> 1065 (5.32%) had protein on the first examination, in amounts ranging from a trace (1+) in 841 to a heavy cloud (3 or 4+) in 64. On re-examination approximately three-fourths of those with a trace on entrance had become free, whereas of those with a heavy cloud, only 6% had become free. The authors found, on comparing 455 proteinuric students with 480 protein-free controls, that the first group was "but little inferior physically" to the second.

Using the heat and acetic acid test, Burden<sup>11</sup> studied a group of 3642 students entering the University of Pennsylvania: 949 (26%) had proteinuria; 69.3% were positive on the first examination only; 6.4% (61 cases) were tested for orthostatic changes, with positive results in 26.

Of 4500 Viennese youths aged 14 to 17 examined by Nowak,<sup>33</sup> 26 (0.8%) were stated to have nephritic proteinuria, and 524 (11.6%), the intermittent type, though criteria and methods were not given. Nowak was unable to demonstrate any relationship between lordosis and proteinuria. There were 2 unusual cases who excreted proteinuria persistently, day and night, on repeated examinations, and never any sedimentary changes of nephritis; both had some kyphoseoliosis and were placed in the non-nephritic group. Another boy, 14 years old,

diagnosed at the first examination as orthostatic proteinuria, had persistent albuminuria and cellular elements of nephritis a year later, with no known episode of acute nephritis intervening.

After 25 years Bashford<sup>4</sup> reexamined some 30 men who had had proteinuria when 14 to 16 years of age. All were in good health; only 1 still had protein in the urine. There was 1 other case, a man who had died 7 years after the initial examination, of "acute nephritis."

Blatherwick<sup>10</sup> reported on the urine findings in 15,000 employees of the Metropolitan Life Insurance Company (Kingsbury-Clark method), a group representative of the general population as regards age and sex distribution and state of health: 91.6% were negative, 3.3% had 10 mg. of protein, and only 1.7% had 20 mg. or higher.

In 1941, Lyall<sup>28</sup> reported on 20,000 men examined during recruitment for the British Armed Services, using the Esbach test: 110 (0.55%) had proteinuria. Of these, 31 exhibited no other findings; 22 were classed as *persistent albuminuria* without evidence of nephritis, though 9 had hypertension or transitory hematuria; 14 men were classed as *subacute nephritis*, 31 as *chronic* or *sclerotic nephritis* and in 12 the source of the protein was distal to the kidney, in renal stone, cystitis, or urinary tract infection.

In 1944, Murphy<sup>32</sup> reported that of 9994 men between the ages of 17 and 50 applying for enrollment in the U. S. Navy, the incidence of proteinuria was 3%; 85% were designated as orthostatic, 13.7% as pathologic and 1.3% as undetermined in type. Orthostatic proteinuria occurred almost exclusively in the younger age groups, being 5.1% in the 4517 who were 17 years old; no cases were discovered in men over 32. A seasonal variation was described, the highest incidence being in the summer months. "Postural defects were common, true lordosis or the lordotic posture being present in over 80% of the cases."

Another reason for giving a good prognosis to intermittent proteinuria is the rapid decline in its frequency with increasing age beyond adolescence. In Harvard freshmen of an average age of 18, proteinuria occurred in about 5%, according to Lee,<sup>25</sup> whereas in upper classmen, with an average age of 20, the incidence was but 3.5%. Diehl and McKinlay's<sup>18</sup> college freshmen were 5.32% positive, whereas MacLean's<sup>29</sup> group of soldiers, older in age, gave but 2.2% positive specimens. In Thorpe and Wakefield's<sup>38</sup> 100 Mayo Clinic patients with age range 4 to 47 years, 26 were 12 years or less, 67 were between 12 and 30, and only 7 were 30 or over. The average age was 18 years. In 64 cases of orthostatic proteinuria collected by Young, Haines and Prince<sup>41</sup> from the Johns Hopkins Hospital files, the ages ranged from 9 to 39 years, most being between 14 and 18 years.

Still another reason is the experience of actual follow-up studies on individual patients. Palmer<sup>34</sup> tracked down 35 former college students who with the nitric acid ring test had once had proteinuria. After 8 or more years but 2 still had traces of protein in the urine. Of 35 others replying to a questionnaire 10 years after the original finding, none had symptoms of renal disease.



When Thorpe and Wakefield<sup>38</sup> reexamined 64 orthostatic cases after an average interval of 7 years, all but 1 were in good health. Of 18 cases that had had persistent proteinuria with an orthostatic increase, only 2 showed renal disease an average of 7.7 years later; the urine of the remaining 16 had become entirely negative. Nor did any of Lee's<sup>26</sup> students with proteinuria develop nephritis over a 5-year observation period. Of 14 orthostatic patients followed by Young *et al.*,<sup>41</sup> 4 were protein-free after 2 years, 6 after 3 years, 1 after 6 years, and 3, 12 years later.

Evers,<sup>20</sup> in 1935, reported that insurees of the New York Life Insurance Company who had had proteinuria without casts or other evidences of nephritis, after 9 years showed no increase in mortality above normal expected levels. Similarly, Christiernin, Dublin and Marks,<sup>13</sup> in a survey of policies issued by the Metropolitan Life Insurance Company from 1925 to 1935, and studied in 1937 and 1938, found no unusual mortality in otherwise normal proteinuric individuals, although when the proteinuria had been associated with hypertension or obesity the mortality was much above normal expectation.

The figures for these large groups of normal individuals are not strictly comparable with each other, nor with the data which follow. The populations studied have not been identical from the standpoints of race, locality, or age and sex distribution, and techniques of testing and criteria taken to delimit proteinous from normal urine have been far from uniform. Only Ashburn, Burden and Murphy endeavored to carry out specific postural studies. The reports emphasize, nevertheless, that uncomplicated proteinuria occurs much more frequently than does nephritis or other forms of kidney disease, and that it is primarily a transitory disturbance of youth.

Thus, without denying that some individuals with intermittent proteinuria may have diminished renal function when standing in the lordotic posture,<sup>40</sup> it seems clear that any "injury" of the kidney responsible for such proteinuria is minor and transitory and quickly recovered from. An essential distinction exists between temporary reversible dysfunctions and more chronic continuing disease states. To generalize from the evidence now at hand, *when careful study reveals no signs of nephritis or urologic disease, particularly in a young subject, simple proteinuria of the intermittent type must be interpreted as a benign innocuous phenomenon.*

**Clinical Material and Methods.** The population group studied for proteinuria consisted of a consecutive series of 22,000 inductees received at the U. S. Maritime Service Training Station, Sheepshead Bay, N. Y., between Sept. 1, 1943, and June 1, 1944. These were fresh recruits drawn from all ranks and occupations of civil life. The majority came from the section of the United States bounded by the Rocky Mountains, Georgia and Canada. All were in supposedly good health on arrival, each enlistee having been examined and passed by Medical Officers in enrollment offices. Their ages ranged from 16 to 50 years. Two-thirds were below 26 years of age; approximately one-half were 20 years of younger (Table 1). Their urine specimens were

collected for analysis about 24 hours following arrival, after breakfast or in the early afternoon, on a day free from undue physical activity.

TABLE 1.—DISTRIBUTION OF 420 PROTEINURIA CASES  
(1.9% of 22,000 Apparently Healthy Trainees)

Classification	No. of cases	Distribution of 400 investigated cases (%)
Intermittent . . . . .	382	95.5
Continuous . . . . .	7	1.8
Nephritic . . . . .	8	2.0
Urologic . . . . .	3	0.7
Total completely studied . . . . .	400	100.0
Study not completed . . . . .	20	
Total . . . . .	420	

Preliminary screening for proteinuria was carried out with Robert's nitric acid-magnesium sulfate ring test. With this test a concentration of 25 to 30 mg. protein per 100 ml. of urine, read usually as "trace"\* gives an opalescent ring of precipitated protein dense enough to be recognized without a black background. All protein-containing specimens positive at or above this threshold level were tested again with the Kingsbury-Clark<sup>24</sup> quantitative technique, in which turbidity produced by adding sulfosalicylic acid to urine is proportional to the quantity of protein present and can be measured against calibrated standards. This method is used by most insurance companies since it is peculiarly suitable for urines containing but small amounts of protein.<sup>10</sup>

Every man with proteinuria of 30 mg. or higher in the above initial examination was recalled. If later urines were negative further tests were not made, whereas if the proteinuria persisted for several successive specimens a 24-hour "orthostatic exercise" test was performed, as follows:

The bladder was emptied 1 hour after going to bed in the evening. Next morning, before rising, another urine specimen was secured. The subject then stood in the lordotic position for 30 to 45 minutes, leaning back at about a 135° angle. After voiding a third specimen, he went about the usual training routine. No fluids were taken during this day (no water, tea, coffee, soft drinks, milk, soup and so forth) in order to secure information on renal concentration power from the specific gravity determinations. All specimens passed through the day were collected and tested individually.

Subjects in whom proteinuria was present constantly even when lying down, or who exhibited abnormal sediments of red cells, leukocytes, or more than a few casts were admitted to the adjoining U. S. Public Health Service Hospital to be observed for nephritis or urinary tract lesions.

\* Terms used in recording "urinary albumin" tests vary greatly in different laboratories. The scale of comparison recommended for the Army (Laboratory Methods of the United States Army, edited by J. S. Simmons and C. J. Gentzkow, Lea & Febiger, Philadelphia, 1944) reads as follows:

Faint trace ( $\pm$ ), less than 10 mg. per 100 ml.; trace (+), 10 to 40 mg.

Small amount (++), 100 mg.; moderate amount (+++), 200 to 300 mg.; large amount (++++), more than 500 mg.

**Classification and Frequency of Proteinuria.** In the initial specimens, 420 of the 22,000 inductees (1.9%) gave urine protein concentrations of at least 30 mg. per 100 ml. Of these men, 20 were transferred or discharged from the Service before the studies could be completed. After diagnostic study the remaining 400 were classified as: (a) *intermittent* proteinuria, 382 instances, (b) *continuous* proteinuria without any associated changes, 7 instances, (c) *nephritic* proteinuria, 8 instances, and (d) *urologic* proteinuria, 3 instances (Table 1). The data are summarized in the ensuing paragraphs, along with discussions of nosologic criteria, age distributions, concentrations of urinary protein and noteworthy features encountered.

*Intermittent Proteinuria.* Under this heading have been placed 382 men whose urines were at times protein-containing and at other times protein-free. None of these had a history of antecedent nephritis; all showed normal sediment in the urine on repeated examinations and were free from hypertension and constitutional findings indicative of renal disease.

Of these, 192 had protein and gave one or more protein-free specimens after the first positive specimen. The urine protein concentrations varied from 30 mg. to 350 mg. per 100 ml., with a mean of 66 mg. 89 others had protein in 2 or more successive random specimens, and then gave negative tests thereafter; their range of protein concentration spread up to 400 mg. per 100 ml. with a mean of 70 mg. With a few of these men some transient irritative stimulus such as an acute infection or physical strain or the excitement accompanying the change from civil to barracks life may have evoked a brief period of proteinuria. With others albuminous fluid from seminal vesicles, prostate or urethra may have contaminated the urine transiently. With most, however, if not all, the proteinuria would undoubtedly have been found to be recurrent and remittent if they had been observed over a continuous 24 hour period, as were those described in the next paragraph.

The remaining 101, after passing 2 or more positive specimens, were subjected to the "orthostatic" exercise routine of study. Every one was found to exhibit proteinuria at least once during this 24 hour observation period. In 83 of these the proteinuria conformed in general with the accepted criteria for orthostatic albuminuria: When they were lying down the urine was protein-free; when upright or lordotic, proteinuria was constant or intermittent. In the other 18 the urine was protein-free during the daytime hours, but contained small amounts of protein in the night urine, with a definite rise after taking the lordotic exercise. Of the whole group, 6 had intermittent excretion of protein in one 24 hour period, but some days later when the test was repeated gave an entirely negative series of specimens.

The concentrations of protein in the urine of these 101 men varied widely, the values for single specimens ranging from 10 to 3000 mg. per 100 ml. urine. The *averages* for the protein-containing specimens of each subject per 24 hours had extremes of 15 and 545 mg., and a grand mean of 74 mg. per 100 ml. Nine individuals produced single specimens containing more than 200 mg. of protein per 100 ml.

The above figures were gathered while the fluid intake was restricted as recommended by Derow.<sup>16</sup> Every subject was able to excrete urine of high specific gravity, showing that the concentrating power of such proteinuric kidneys was not impaired to any extent. The range for the individual maximum specific gravity figures was 1.025 to 1.034, with a mean of 1.029.

These 382 subjects seemed to possess the clinical variety of proteinuria best called intermittent, though known also as physiologic, periodic, postural, orthostatic, orthotic, lordotic, cyclic, juvenile and so forth.<sup>12,23,25,36,41</sup> The condition is fairly common during childhood, attains maximum incidence in adolescence and then declines in frequency as adult maturity is reached.<sup>23</sup> The present series (Table 2) demonstrates the latter half of this cycle. At 16 years of age the incidence was highest, 4.6%; at 17 years, it became 3.08%; at 18, it was down to 1.61%.

TABLE 2.—THE AGE FACTOR AS RELATED TO PROTEINURIA (400 CASES)

Age (yrs.)	No. of trainees	Intermittent		Con- tinuous	Neph- ritic	Uro- logic	Total	
		No.	% of age group				No.	% of age group
16-20	11,822	300	2.54	1	4	3	308	2.61
16	2632	121	4.60		1		122	4.64
17	1948	60	2.08		1	1	62	3.18
18	5208	95	1.61	1	2	2	100	1.92
19	1167	16	1.37				16	1.37
20	867	8	0.92				8	0.92
21-25	3,719	27	0.73	1	3		31	0.83
26-30	3,798	28	0.74	3			31	0.82
31-35	2,127	17	0.80	2			19	0.89
Over 35	534	10	1.87		1		11	2.06
Totals	22,000	382	1.74	7	8	3	400	1.82

None of these subjects had undernutrition or a skeletal deformity, and all had satisfactorily passed the thorough physical examination required for entry into the Maritime Service. The Station orthopedist\* compared the habitual position of the spine in a series of 100 intermittent proteinuric trainees with an equal number of non-proteinuric trainees, and failed to uncover any differences between the two groups in the incidence of lordosis and other postural faults. The amount of lordosis of the lumbar spine was determined clinically by means of inspection and palpation, using arbitrary symbols 1+, 2+ and so forth as criteria of comparison. The data when tabulated were as follows:

Amount of lordosis of lumbar spine:	0	1+	2+	3+	4+	Total
Controls	46	31	15	6	2	100
Intermittent proteinuria	41	26	19	12	2	100

Thus the control group had 54% with lordosis and the proteinuria group had 59% with lordosis. When rearranged into groups according to severity of lordosis, no significant difference was evident between the proteinurics and the controls. These observations do not controvert

\* Dr. Renato Ricca, Asst. Surgeon, U. S. Public Health Service (Reserve).

the well-established pathogenetic relationship which can exist between lordosis and proteinuria—indeed, most of the present group of cases excreted more protein when placed temporarily in the lordotic position. Instead, they demonstrate that with non-lordotic individuals other factors can excite escape of protein into the urine.

For the reasons given in the preliminary discussion all inductees having such uncomplicated intermittent proteinuria were permitted to proceed in training without restriction.

In passing, it is of interest to record that with many men who exhibited proteinuria during and immediately after the "orthostatic exercise," the clearing of the voided specimens took place gradually and stepwise when they were made to lie down after spending 30 to 45 minutes in the lordotic position. In successive specimens collected at 30 minute intervals traces of protein were in a few instances still present after 3 hours. This lag in disappearance of the protein was probably due to incomplete emptying of the bladder during voiding, permitting some of the earlier lordotic urine to remain and mix with later recumbent urine flowing in from the ureters. The factor of incomplete bladder emptying was not considered in a recent recommendation<sup>17</sup> for quick differentiation of albuminuric Army inductees by collection of but 2 specimens, 1 immediately after lordotic exercise, the second,  $\frac{1}{2}$  hour later.

Murphy<sup>32</sup> very recently has reported that proteinuria in his series of Navy applicants was more frequent in July and August than later in the year. To check his observation this Station's figures for the months of June through September 1944 were reviewed. The frequency of proteinuria for all new trainees, expressed in round numbers, was as follows: June, 2.6%; July, 5.2%; August, 6%; September, 3.5%. The distribution of the new trainees as regards the age factor was approximately the same for each of these months. It did not seem wise to draw conclusions for earlier than June, inasmuch as the Station, prior to that month, had not taken in men under 18 years of age in appreciable numbers, whereas from June 1 onward nearly 75% of the inductees were younger than 18 years. These limited data, so far as they go, substantiate Murphy's finding. The phenomenon of seasonal variation seems not to have been reported heretofore; no doubt it is related in some way to the almost universal production of urine of high specific gravity and reduced volume during the heat of the summer.

*Continuous Proteinuria.* Seven men had protein in all specimens collected. Five were 25 to 27 years of age, 1 was 18 and 1 was 31. Two were moderately overweight; the others were slender. None gave a history of antecedent nephritis. One had a weak positive serology titer for syphilis, without any clinical signs of the disease. One patient, aged 26 years, when subjected to 5 separate 24 hour "orthostatic" studies had protein in all but 2 sporadic specimens collected on different afternoons. Another patient's proteinuria had been first recognized 7 years earlier. Blood pressures and other findings were normal in all. In single specimens the range of protein

extended from a minimum concentration of 10 mg. to a maximum of 600 mg. per 100 ml. Recumbent values were not much lower than those during activity. The mean figures for all the tests on each individual were, in increasing order, 45 mg., 51 mg., 51 mg., 56 mg., 81 mg., 216 mg., 250 mg.\* A few white cells and hyalin casts were found sporadically in the urine of each. On concentration tests, 4 produced urines of 1.030 specific gravity, 1 attained 1.025, 1 was 1.021 and 1 was not tested. Renal function tests showed no noteworthy impairment. Addis sediment counts done repeatedly on the urines of 5 of the 7 proved normal in every instance. Intravenous pyelograms performed on 5 showed normal uteropelvic patterns.

Because of the suggestion<sup>6,9,35</sup> that alkalization of the urine may clear the urine in functional but not in nephritic proteinuria, sodium bicarbonate was administered to 2 subjects. Their proteinuria ceased temporarily to recur as soon as alkalization was stopped. Enough exceptions occur both ways<sup>18,21</sup> to negate the value of this phenomenon as a diagnostic test.

Since these 7 men with continuous proteinuria showed no indications of renal dysfunction apart from the proteinuria, and since there were no other data to connote antecedent nephritis or latent chronic renal disease, they were permitted to proceed with training and to go out to sea on merchant vessels. Inasmuch as recruits remain at this station but a relatively short time—1 to 5 months—no opportunity exists for observation of the ultimate outcome of their proteinuria. Murphy<sup>32</sup> found 4 apparently similar instances among 9994 Navy recruits. These were all 17 years of age; displayed proteinuria not affected by postural changes; and had no other noteworthy features.

No evidence was encountered to suggest that kidneys which leak protein are unusually susceptible to the toxic agents that induce glomerulonephritis. MacLean<sup>29</sup> had found the distribution of "trench nephritis" to be no higher among troops who had exhibited a positive protein test earlier in the campaigns than among those whose urines had been negative. A similar generalization may be drawn from the present study. Of 27 cases of acute glomerulonephritis and 7 cases of acute pyuria which developed among the 22,000 recruits subsequent to entry on the Station, not one single instance came from the group of 420 individuals who had manifested proteinuria in the initial arrival urinalysis.

*Nephritic Proteinuria.* The diagnosis of mild or latent nephritis was made in 8 instances. All had mild hematuria and abnormal quantities of red cells and casts in Addis counts. All showed protein in every specimen examined, including those collected while recumbent. Several had diminished phenolsulphonephthalein excretion, slight elevations of blood pressure, and other evidences of impaired renal function. In age, 7 were between 16 and 24 years; the eighth was 37 years old. The concentration of urinary protein per 100 ml. in their admission specimens were, respectively, 30 mg., 40 mg., 75 mg., 200 mg., 200 mg., 280 mg., 375 mg., 725 mg.

On physical examination these subjects did not appear ill and were

\* See footnote, page 91.

unaware of the existence of the renal lesions. Diagnosis of the exact kind of nephritis was not feasible in view of the absence of opportunity for long-range follow-up of their progress. However, these men were all given discharges from the Maritime Service by the Medical Board because of the probable chronic nature of the condition and the possibility of serious complications which might interfere with training and later sea duty.

*Urologic Proteinuria.* Three disturbances in the realm of urology were uncovered by the initial urine examination. There was 1 case of acute cystitis and 1 of gonorrheal urethritis, both of which cleared under treatment; and 1 case of hydronephrosis which was discharged from the Service. With each of these the entrance urine specimen contained but a trace of protein, 30 mg. per 100 ml.

*In Summary.* Of a total of 400 recruits studied for proteinuria, 382 had the benign intermittent type and 7 the continuous type, probably benign; 8 had asymptomatic nephritis; 3 had urologic disturbances. Only the 7 nephritis cases and 1 urologic case were discharged from the Service; with the remaining 392 (98%), the proteinuria was adjudged no handicap to training. The other 20 men in the full series of 420 were not adequately studied.

*Concentration of Protein in the Urine.* It is, of course, well known that nephrotic patients and those ill with acute or severe nephritis may show high concentrations of urinary protein, from 1 to 5 gm. per 100 ml., or higher. However, as already discussed, in the milder forms of organic renal disease the levels may be lower, and usually are, ranging down to complete absence of protein when the subject is recumbent. The protein then appears only with change from the resting position.

Physicians often inquire whether one can utilize the information concerning the amount of protein in one random sample of urine as an aid in diagnosis. Since the present group of cases is apparently the first large series in which the protein content of single specimens has been scored in direct quantitative measurements rather than by the crude and confusing "number-plus" system, it is of interest to review the data from this standpoint. The findings are tabulated in Table 3, along with the ranges and mean concentrations of protein as encountered in continuous, nephritic and urologic proteinuria. The 3 urologic cases had a mean of 30 mg. per 100 ml.; the intermittent cases, 70 mg. per 100 ml.; the continuous cases, 107 mg.; and the chronic nephritis cases (admission urine) 240 mg.

TABLE 3.—CONCENTRATION OF PROTEIN IN URINE WITH DIFFERENT TYPES OF PROTEINURIA

Classification	No. of cases	Observed range of individual specimens (mg. per 100 ml.)	Mean (mg. per 100 ml.)
Intermittent . . . . .	382	10-3000	70
Continuous . . . . .	7	10- 600	107
Nephritic (initial specimens) . . . . .	8	30- 720	240
Urologic . . . . .	3	30- 30	30

Thus the magnitude of the concentration of protein in a single specimen of urine is unreliable as a major criterion for distinguishing among

the various types of proteinuria. Indeed, the specimen richest in protein encountered in this study (3000 mg. per 100 ml.) came from a 19 year old with inconstant proteinuria, whereas 3 of the 7 cases of nephritis had protein concentrations on admission which were as low or lower than the grand mean value for the intermittent group of cases. Viewed statistically, however, the most serious disturbance had the highest average value.

In chronic nephritis, Berglund, Scriver and Medes<sup>6,9,35</sup> noted the rate of protein excretion to be independent of fluid intake and output, urine specific gravity or urine protein concentration, though a temporary increase may follow a change from rest to active walking, or a more permanent rise accompany the change from a low to a high protein diet. In other words, under constant conditions of physical activity the protein excretion per hour remained about the same regardless of whether there was a diuresis or a highly concentrated oliguria. Hence it is not possible to estimate the total daily excretion of protein from the amount in a single urine sample, unless the rate of urine secretion is known also. In acute nephritis, on the other hand, Berglund and Frisk<sup>5</sup> and Bing<sup>7</sup> have noted that the proteinuria is subject to quick inexplicable changes, irrespective of diet, particularly in the direction of improvement.

Many life insurance firms<sup>15</sup> now no longer refuse policies to prospective policyholders who are in good health apart from small quantities of protein in the urine. The threshold level has been set at about 50 to 75 mg. of protein per 100 ml. of urine to delimit "harmless" from "suspicious" proteinuria, the precise figure varying with different companies. The errors inherent in the use of such arbitrary limits are obvious from the preceding discussion: many subjects with benign intermittent proteinuria come above these values, occasional mild nephritis cases produce protein concentrations below 50 mg. per 100 ml., and by rest, forcing fluids and ingestion of alkali a canny applicant can temporarily reduce a moderate albuminuria of whatever etiology to a low level or make it disappear altogether.

**Reliability of One Urine Analysis for the Detection of Proteinuric Disorders.** A so-called routine urinalysis is an essential component of any good physical examination. One purpose of this test is to detect manifestations of renal disease and related disorders.

The records of the 22,000 trainees have been scrutinized to ascertain the trustworthiness of a single urine examination as a screen for the detection of nephritis, urologic disorders, and benign proteinuria.

**Nephritis.** The routine admission urine analyses brought to light 8 cases of nephritis, all mild, symptom-free and unsuspected. During the subsequent 1 to 5 months that the 22,000 recruits remained on the Station for training, not another instance of preëxisting nephritis came to the notice of the medical staff even though at one time or another nearly every man had occasion to seek medical service either in his barracks sick-bay or at the base hospital. Mention has already been made of the 27 men who became ill with acute postinfectious glomerulonephritis during their training; not one showed protein in the original urine specimen collected on arrival.



Inasmuch as protein escapes almost continually into the urine during nephritis, any one urinalysis carefully done should reveal its presence. Only when a patient has nearly recovered from an acute attack or is in a subclinical phase of long-standing chronic glomerulonephritis does the proteinuria of nephritis become irregular and inconstant; in those exceptional cases erythrocytes and casts in the sediment are present to indicate the diagnosis.

*Urologic Disturbances.* Only 3 such cases were caught by the initial screening test. Later, during training, 17 other subjects came forward with major urinary tract disorders which must have been existent on arrival, though their initial examinations were negative. Three of these had infected hydronephrosis, 5 had major anomalies of one kidney, usually with associated infection, 4 had disturbances of the ureters or bladder, and 5 had renal calculi. Most of the infection cases had to be discharged and sent home. Thus it is obvious that urologic lesions will often be missed if reliance is placed on a single urine examination.

*Benign Proteinuria.* Of the 22,000 men, 1.8% exhibited benign proteinuria in the initial specimen. 2.5% were 18 years old or younger, and the age factor played a significant rôle. Some had exhibited but 1 positive specimen followed by 1 or more negatives, whereas others had shown 2 or more proteinous specimens before negative ones were secured. It was noted further that the intermittency or inconstancy of the proteinuria is one cardinal urologic difference between this kind of proteinuria and active nephritis. The question naturally arises, how often would this fluctuant disturbance escape detection in a single routine urinalysis?

To get a truer picture of the frequency of proteinuria in healthy men, a more intensive study\* was carried out on a group of 110 trainees. Over a 5 day period 8 separate urine specimens were collected from each, at noon and late afternoon for 3 days, and then on the following days at noon. During this experiment the men were physically active, occupied with drill, swimming and busy work assignments. Sixty-six were 16 years old; the age distribution of the remainder paralleled roughly that of the basic population of 22,000. *Not one had had protein in the initial specimen collected at the beginning of training.*

Tabulation of the 8 analyses yielded an unexpected high frequency of proteinuria. Of the 110 men, 62 (56%) produced at least 1 protein-containing specimen, and 14 (13%) had protein in more than half of the specimens collected. The exact figures were:

Positive	Negative	Instances
8	0	2
7	1	3
6	2	2
5	3	7
4	4	11
3	5	7
2	6	9
1	7	21
0	8	48

\* These determinations were done with the photo-electric colorimeter, which adapts itself most efficiently to the measurement of precipitation turbidity.

The occurrence of positive tests was not significantly higher for the 16 year old fraction of the group than for the more mature trainees. The highest protein-containing specimen had a concentration of 328 mg. per 100 ml. and there were 9 others over 100 mg. per ml. However, the great majority of the readings fell in the 20 mg. to 60 mg. zone, the over-all mean being 52 mg. per 100 ml. The bulk of the readings thus corresponded to 1+ in the semiquantitative code for recording protein in urine. The microscopic examinations were all negative. Typhoid vaccine inoculations received in the middle of the week of study did not evoke a wave of proteinuria.

Thus, if 62 of 110 men, even though the majority are youthful, will display proteinuria once or oftener when studied with multiple urinalyses, then obviously intermittent proteinuria is much more prevalent in the general population than indicated by text-book statistics compiled from random single tests.

To conclude, *a random urine specimen can be depended upon nearly always to bring to light active nephritis if present, since in this disease, save in a few exceptional phases, protein and pathologic sediments are being excreted constantly day and night into the urine. In contrast, chronic urologic disturbances and benign intermittent proteinuria are subject to frequent intermissions. To establish their presence or absence one needs a fair number of specimens collected during different stages of physical activity.*

**Summary.** Urine examinations performed on 22,000 presumably healthy American men entering the U. S. Maritime Service revealed proteinuria in 420 (1.9%). In most instances, representing 1.7% of the original group, the proteinuria was intermittent or "orthostatic," with incidence highest at age 16.

The remaining cases in the series had either continuous proteinuria due to no elicitable cause, or mild unsuspected nephritis, or urologic disease.

Review of the cases and of the observations on record indicates that intermittent proteinuria in the age period covered is a harmless benign condition, provided there are no associated clinical or urinary changes.

In the study of disturbances accompanied by proteinuria, the concentration of protein in random specimens of urine is not helpful as a diagnostic guide.

In random urinalysis of single specimens nephritis will usually reveal itself. But more cases of urologic or benign intermittent proteinuria will be missed than caught.

#### REFERENCES

1. ADDIS, T.: J. Am. Med. Assn., 85, 848, 1937.
2. ASHBURN, P. M.: J. Am. Med. Assn., 90, 535, 1928.
3. ATLEE, W.: Laneet, 2, 717, 1934.
4. BASHFORD, H. H.: Praetitioner, 135, 272, 1935.
5. BERGLUND, H., and FRISK, A. R.: Acta med. Scandinav., 96, 255, 1938.
6. BERGLUND, MEDES, et al.: The Kidney in Health and Disease, Philadelphia, Lea & Febiger, 1935.
7. BING, J.: Acta med. Scandinav., 88 Suppl., 76, 1936.
8. BLACKMAN, S. S., JR., GOODWIN, W. E., and BUELL, M. V.: Bull. Johns Hopkins Hosp., 69, 397, 1941.

9. BLACKMAN, S. S., JR., and DAVIS, D.: *J. Clin. Invest.*, 22, 545, 1943.
10. BLATHERWICK, N. R.: *South. Med. and Surg.*, 104, 86, 1942.
11. BURDEN, N. J.: (a) *Penna. Med. J.*, 37, 32, 1933; (b) *Am. J. Med. Sci.*, 188, 242, 1934.
12. CALVIN, J. K.: *J. Pediat.*, 4, 611, 1943.
13. CHRISTIERNIN, C. L., DURLIN, L. I., and MANKS, H. H.: *Abstr. Proc. Assn. Life Ins. Med. Dir. America*, 26, 160, 1940.
14. CSATARY, A.: (a) *Deutsch. Arch. f. klin. Med.*, 47, 159, 1890; (b) *Ibid.*, 48, 358, 1891.
15. DALEY, R. M.: *Albuminuria and Insurability*, *Urol. and Cutan. Rev.*, 46, 13, 1942.
16. DEROW, H. A.: *New England J. Med.*, 227, 827, 1942.
17. DEROW, H. A., and STELLAR, L. I.: *J. Am. Med. Assn.*, 123, 503, 1943.
18. DIEHL, H. S., and MCKINLAY, C. A.: *Arch. Int. Med.*, 49, 45, 1932.
19. ELWYN, H.: *Nephritis*, *Cyclopedia of Medicine, Surgery and Specialties*, Philadelphia, F. A. Davis, 8, 412, 1939.
20. EVERS, F. C.: *Abstr., Proc. Assn. Life Ins. Med. Dir. of America*, 22, 8, 1935.
21. FISHER, A. M.: *Hypertension and Nephritis*, Philadelphia, Lea & Febiger, 1939.
22. HENNST, R.: *Ztschr. f. arztl. Fortbild.*, 35, 314, 1938.
23. JEHLE, L.: *Ergebn. d. inn. Med. u. Kinderheilk.*, 12, 15, 1913.
24. KINGSBURY, F. B., CLARK, C. P., WILLIAMS, M. I., and POST, A. C.: *J. Lab. and Clin. Med.*, 11, 981, 1926.
25. LAUENER, P.: *Schweiz. med. Wchnschr.*, 52, 1170, 1922.
26. LEE, R. I.: *Med. Clin. North America*, 3, 1059, 1920.
27. LUETSCHER, J. A.: *J. Clin. Invest.*, 29, 313, 1940.
28. LYALL, A.: *Brit. Med. J.*, 2, 113, 1941.
29. MACLEAN, H.: *Albuminuria and War Nephritis Among British Troops in France*, *Med. Res. Coun. Great Britain, Sp. Report No. 43*, 1919.
30. McLEOD, J. R., and AMEUILLE, P.: *Lancet*, 2, 465, 1916.
31. MÖRNER, K. A. H.: *Skand. Arch. Physiol.*, 6, 332, 1895.
32. MURPHY, W. A.: *U. S. Naval Med. Bull.*, 43, 321, 1944.
33. NOWAK, H.: *Monatschr. f. Kinderheilk.*, 59, 341, 1933.
34. PALMER, R. S.: *J. Am. Med. Assn.*, 96, 1559, 1931.
35. POST, W. E., and THOMAS, W. A.: *J. Am. Med. Assn.*, 80, 293, 1923.
36. PRINCE, C. L.: *J. Urol.*, 50, 608, 1943.
37. RYTAND, D. A.: *Arch. Int. Med.*, 59, 163, 1925.
38. THORPE, E. G., and WAKEFIELD, E. G.: *Ann. Int. Med.*, 6, 1565, 1933.
39. WANG, C. F., and WU, H.: *Chinese J. Physiol.*, 12, 371, 1937.
40. WHITE, H. H., ROSEN, I. I., FISCHER, S. S., and WOOD, G. H.: *Am. J. Physiol.*, 78, 185, 1926.
41. YOUNG, H. H., HAINES, J. S., and PRINCE, C. L.: *Mil. Surg.*, 92, 353, 1943.

## ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH LESIONS IN THE DEEPER LAYERS OF THE MYOCARDIUM

### AN EXPERIMENTAL STUDY\*

By RAYMOND D. PRUITT, M.D.

MEMBER OF DIVISION OF MEDICINE

ARLIE R. BARNES, M.D.

DIVISION OF MEDICINE, MAYO CLINIC

AND

HIRAM E. ESSEX, Ph.D.

DIVISION OF EXPERIMENTAL SURGERY AND PATHOLOGY  
ROCHESTER, MINN.

(From the Division of Medicine, Mayo Clinic, and the Division of Experimental Surgery and Pathology, Mayo Foundation)

THERE exists a considerable amount of knowledge relative to the ECG's effect of myocardial damage involving either the epicardium

\* Abridgment of thesis submitted by Dr. Pruitt to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine.

alone or the entire cardiac wall. Until recent years, no intensive study of the ECG effects of lesions confined to the deeper layers of the myocardium had been carried out, but recently efforts have been made to clarify this phase of electrocardiography.

Boyd and Scherf<sup>2</sup> (1940) in 17 experiments on dogs scarified the inner surface of the left ventricular apex with a sound introduced through the left auricle. No striking modifications in standard lead ECG's occurred after this procedure. The maximal effects were represented in a series of tracings in which there was a slight depression of the RS-T segment in Leads II and III and a reversal in the direction of the T wave in all 3 standard leads. Even these changes disappeared within 6 minutes.

Kisch, Nahum and Hoff<sup>5</sup> (1940), on the basis of experiments in which potassium chloride was applied to the surface or injected into the muscle layers of the hearts of dogs, cats and rabbits, suggested that "The magnitude of the ECG changes following injury to the heart is almost entirely conditioned by the nature, extent and location of the surface involvement. It is possible that the electrical activity of the ventricles is a phenomenon which is determined largely by the surface of the heart."

Robb and Robb<sup>7,8</sup> (1939) suggested that injury to a specific muscle bundle produces characteristic alterations in standard lead ECG's. Infarction of a specific muscle bundle has ECG consequences of a similar nature regardless of whether the injury to the muscle bundle involves its deep or superficial portion. These workers concluded that distribution of segmental elevation or depression among the standard lead tracings defines the muscle bundle which has been the site of injury.

On the basis of clinical observations, Master, Gubner, Dack and Jaffe<sup>6</sup> suggested that "myomalacia following coronary insufficiency differs as a rule from that following coronary occlusion by its focal and disseminated character and by its localization in the subendocardium and papillary muscles of the left ventricle" and that "the electrocardiogram of acute coronary insufficiency with infarction is characterized by the presence of a depressed RS-T segment and flattening or inversion of the T wave in 2 or more leads." And finally, "The presence of a depressed RS-T segment in acute coronary insufficiency is attributed to the subendocardial localization of the infarction."

For several years in articles on varying subjects, Wilson and associates<sup>3,4,9-13</sup> recorded observations on the contribution of the deeper layers of the myocardium to the ECG. Two of their conclusions follow: In direct leads from regions in which the inner layers of muscle were dead or had been replaced by scar tissue and in which the outer layers were still living and responding to the excitatory process, the QRS group was characterized by specific changes in that portion preceding and including the intrinsic deflection. The RS-T segment was not displaced. On the other hand, Wilson and associates observed that when a sharp electrode was thrust through the ventricular wall into the ventricular cavity, and thence into the subendocardial muscle

of the dorsal wall of the heart, the resulting curves manifested essentially the same pronounced shifts of RS-T segment as occurred when the same type of electrode was introduced into the epicardial layers of the heart.

These several reports have no striking conformity. In 3 of them, the conclusion is that deep myocardial lesions produce either no change in the standard lead ECG or the minor and relatively non-specific alterations represented in slight depression of the RS-T segment and flattened or inverted T waves.

**Purpose of Study.** Our own attempt to define ECG changes that could be regarded as characteristic of lesions limited to the deeper layers of the myocardium was not undertaken in an effort to confirm or disprove any of the foregoing views. Rather, we wished to know whether large areas of myocardial damage could exist without ECG changes of a specific, constantly recurring type. If lesions of this kind occur, a likely site for them is in the subendocardial layers.

**Method. Traumatizing Instrument.** The difficulties of producing a lesion confined to the subendocardial myocardium are obvious. Although several methods were tried, an entirely satisfactory technique was not devised. The mechanical method finally was selected principally because it appeared to afford the only approach that permitted relatively exact localization of lesions. The method has apparent limitations, but if these are recognized the inherent error is not sufficiently great to invalidate the conclusions. Our original intention was to study the ECG effects of deep injuries in both the acute and chronic phases; however, experiments of long duration were abandoned because of limitations of the method.

The traumatizing instrument consisted of a piece of piano wire with a coil of one and a half loops at the end. The shaft of the wire was run through a Luer-Lok needle. To produce a lesion, the coiled portion of the traumatizing instrument was directed into the apical portion of the left ventricle, much as a corkscrew would be driven into a cork. At the conclusion of this initial stage the curved portion of the instrument lay free in the ventricular cavity. By altering slightly the direction of the shaft and allowing it to move through the hilt toward the ventricular cavity, fibers of the subendocardial myocardium could be caught in the revolving loops of the spiral. Gentle traction applied to the shaft usually produced tearing of the fibers enmeshed in the spiral. The greatest single difficulty, as a rule, was encountered on attempting to withdraw the traumatizing instrument. This hazard developed as a result of entanglement of partially severed strands of endocardium in the coils of the instrument. In most instances, little bleeding occurred after withdrawal of the wire and usually this was controlled readily by digital pressure over the bleeding point.

**Material.** Fifty-nine dogs varying in weight from 3 to 57 kg. were used. The majority of the experiments were performed on medium sized animals weighing between 10 and 20 kg. The fact that ECG's of dogs exhibit significant spontaneous variations from day to day is well recognized; however, such variations were not observed in experiments of a few hours duration in which the animals were maintained in a fixed position.

**Anesthetic Agent.** Anesthesia was induced with pentobarbital sodium administered intravenously; 25 mg. per kg. of body weight usually was adequate to induce anesthesia of sufficient degree for a surgical procedure. In order to maintain anesthesia, further pentobarbital sodium was given either intravenously or subcutaneously. That the

induction of anesthesia in dogs by use of pentobarbital sodium produced no significant changes in the ECG is indicated by the carefully controlled experiments of Betlach<sup>1</sup> and by our own experiments in which ECG's were made before and after anesthetization.

*Procedure.* The dog was laid on its right side. The thoracic cavity was entered by an incision through the sixth intercostal space. At this time artificial insufflation was instituted and maintained throughout the remainder of the experiment. A small opening was made in the apical pericardium, but an attempt always was made to maintain the major attachments of the pericardium so that the preoperative relationships of the heart were disturbed as little as possible.

An effort then was made to produce a deep lesion by using the spiral wire technique previously described. Usually the entire procedure was performed in 1 to 2 minutes. If it appeared unlikely that an adequate lesion had resulted from the first attempt, the entire procedure was repeated, usually about 1 hour after the initial attempt.

*Electrocardiograms.* With an ECG (Sanborn cardiette) so standardized that a current of 1 mv. produced a beam deflection of 1 cm., ECG's were taken at the following times: (1) after anesthesia, with the dog fixed in the position to be maintained throughout the remainder of the experiment; (2) after opening the chest and apical pericardium; (3) immediately after traumatizing the heart or carrying out any control procedure; and (4) at varying intervals thereafter.

*Results.* The results, which we regard as significant, were obtained only after use of precordial leads was begun. It is regrettable that in our earlier experiments records were obtained only with the standard leads. In the 59 experiments on dogs, at least 1 precordial ECG was obtained in 25. In this latter group, the exploring electrode was placed at one or at several positions over the precordium. In all cases in which any precordial lead was used, tracings were obtained with the exploring electrode over the cardiac apex and the indifferent electrode on the right foreleg. Connections were so made that a positive potential at the exploring electrode resulted in an upward deflection of the galvanometer beam. This apical lead is comparable, therefore, to the apical IV-R lead in human electrocardiography.

Of the 25 experiments in which at least 1 precordial ECG was obtained, all but 3 are included in this analysis. In 2 of those excluded, the cardiac lesions were small and the ECG changes were minimal. The results are represented adequately in the earlier phases of certain of the more satisfactory experiments in which the final lesion was achieved in 2 or 3 stages. The third experiment was discarded because the dog died before satisfactory ECG's could be obtained. With these exceptions, the following results are the product of 25 consecutive experiments.

*Changes in the QRS Complex.* Alterations of significant degree in the form of the QRS complex in the apical IV-R lead occurred in each of the 22 experiments (Table 1). Many of the following measurements were made on ECG's taken at or near the end of the experiment, sometimes several hours after final traumatizing procedures had been performed. These data, therefore, indicate trends of change rather than instantaneous developments.

TABLE 1.—CHANGES IN THE Q, R AND S WAVES AFTER DAMAGE TO THE DEEPER LAYERS OF THE MYOCARDIUM (Apical IV-R Lead)

Dog No.	Height of R wave (mm.)		Depth of Q wave (mm.)		Depth of S wave (mm.)	
	Pre-trauma	Post-trauma	Pre-trauma	Post-trauma	Pre-trauma	Post-trauma
1 . . . . .	18	4	0	0	2	3
2 . . . . .	17	4	0	0-1	4	13
3 . . . . .	15	<1	0	0	6	3
4 . . . . .	12	1	0	0	4	3
5 . . . . .	20	3	0	0	12	9
6 . . . . .	17	1	0	0	0	11
7 . . . . .	19	2	0	0	2	4
8 . . . . .	11	1	0	0	4	5
9 . . . . .	8	<1	0	0	6	4
10 . . . . .	12	1	0	0	9	15
11 . . . . .	12	2	0	0	3	10
12 . . . . .	13	2	0	0	2	3
13 . . . . .	14	1	0	0	6	10
14 . . . . .	14	0	0	0	6	4
15 . . . . .	22	3	0	0	3	7
16 . . . . .	23	2	0	0	2	7
17 . . . . .	12	23	0	4	0	0
18 . . . . .	14	17	0	0	2	0
19 . . . . .	18	9	0	0	2	0
20 . . . . .	15	8	0	0	5	0
21 . . . . .	16	6	0	4	<1	0
22 . . . . .	30	7	0	3	2	0

Diminution in the height of the R wave after infliction of deep trauma was the change most commonly noted (Figs. 1, 2, 3, 4 and 5). In no instance was the height of this wave before trauma less than 8 mm.; it averaged 15 mm. After myocardial injury, its height decreased to a level less than 4 mm. in 16 of the 22 experiments. In 10 of the 16 instances in which the R wave diminished in height, the S wave became deeper. In only 3 experiments was this increase in depth more than 5 mm. Concerning the other 6 of the 22 experiments, the R wave became shorter in 4 and higher in 2. In every instance in these 6 experiments the S wave disappeared completely and either a notch on the upstroke of the R wave or a Q deflection developed.

Significant widening of the QRS complex after infliction of deep trauma occurred in 2 experiments. In 1 instance (Figs. 6 and 7) this complex in control tracings measured 0.04 second and after trauma 0.08 second, and in the other, 0.05 second and 0.07 second, respectively.

Increased depth of the Q wave in Leads II and III occurred in 7 of the 22 experiments. The Q wave in the control tracings was absent in only 2 of these 7 instances. The greatest increase in depth was 5 mm. The significance of this alteration is reduced by the inconsistency of the presence and size of the Q wave in the control tracings and the relatively minor increase in the depth of this wave following trauma.

Changes in the form of the QRS complex in Lead I were noted frequently. However, the amplitude of the deflections in this lead were invariably small, significantly altered by respiratory movements, and consequently the changes were difficult to interpret.

*Changes in the RS-T Segment.* Significant elevation of the RS-T segment occurred in only 2 of the 22 experiments. In 1 of these, an

unusual amount of surface damage was present. In the other, the deep lesion extended close to the surface of the posterior wall of the left ventricle. However, in 34 earlier experiments not included in this survey, 3 instances of segmental elevation occurred. In at least 1 of these, no unusual degree of surface damage could be identified.

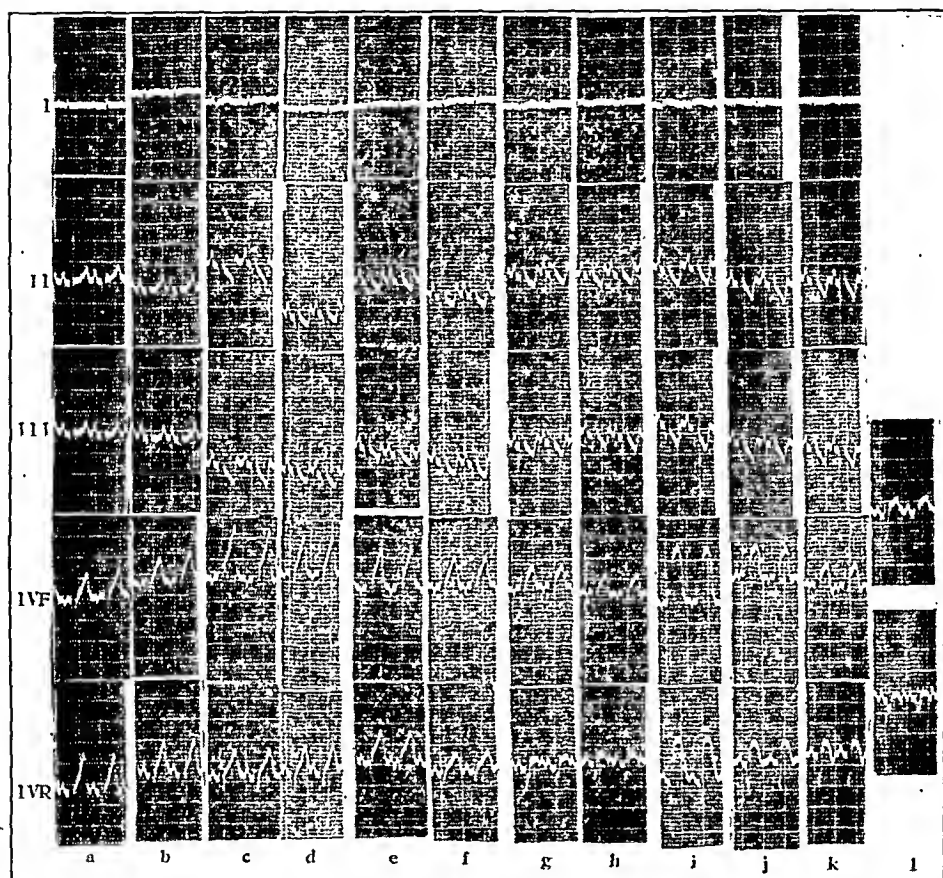


FIG. 1.—Dog 14. Roman numerals and capital letters represent the leads. *a*, Control after anesthesia; *b*, control after opening the chest and pericardium; *c*, 10 A.M., 5 min. after the first attempt at deep trauma (this lesion probably involved the posterior septum and the posterior papillary muscle); *d*, 10:35 A.M., 40 min. after the first attempt at deep trauma; *e*, 10:57 A.M., 5 min. after the second attempt at deep trauma (this lesion probably extended anteriorly across apical septum onto wall of apical portion of left ventricle anteriorly); *f*, 11:50 A.M., 58 min. after the second attempt at deep trauma; *g*, 1:45 P.M., 2 hrs. 50 min. after the second attempt at deep trauma; *h*, 3:15 P.M., 4 hrs. 25 min. after the second attempt at deep trauma; *i*, 3:40 P.M., immediately after a superficial burn was made over an area 2 by 2 cm. on the apex of the left ventricle anteriorly; *j*, 4 P.M., 20 min. after burn; *k*, 4:40 P.M., 1 hr. after burn; *l*, leads from right border of sternum (CR<sub>1</sub>) at level of apex and from point 5 cm. to left of sternum at level of apex (CR<sub>6</sub>) taken at 3:15 P.M.

When segmental elevation occurred, it usually attained its maximal degree in about 30 minutes and then gradually receded over a period of several hours. The diminution in segmental elevation was associated with the development of a deeply inverted T wave. An exception to this usual course of development occurred in 1 experiment, in



which elevation of the RS-T segment in Leads II and III was present in the tracings taken immediately after trauma and persisted undiminished until the animal was killed  $6\frac{1}{2}$  hours later.

The paucity of examples of marked segmental elevation in association with deep myocardial lesions contrasts with the frequency with which this type of change was encountered in experiments in which the anterior apical area of the left ventricle was burned superficially with an electrocautery wire (Fig. 2). Significant elevation of the RS-T segment in Leads I, apical IV-R and apical IV-F occurred in each of 6 experiments in which this latter procedure was executed (Fig. 1). Unlike the changes attending deep lesions, the segmental

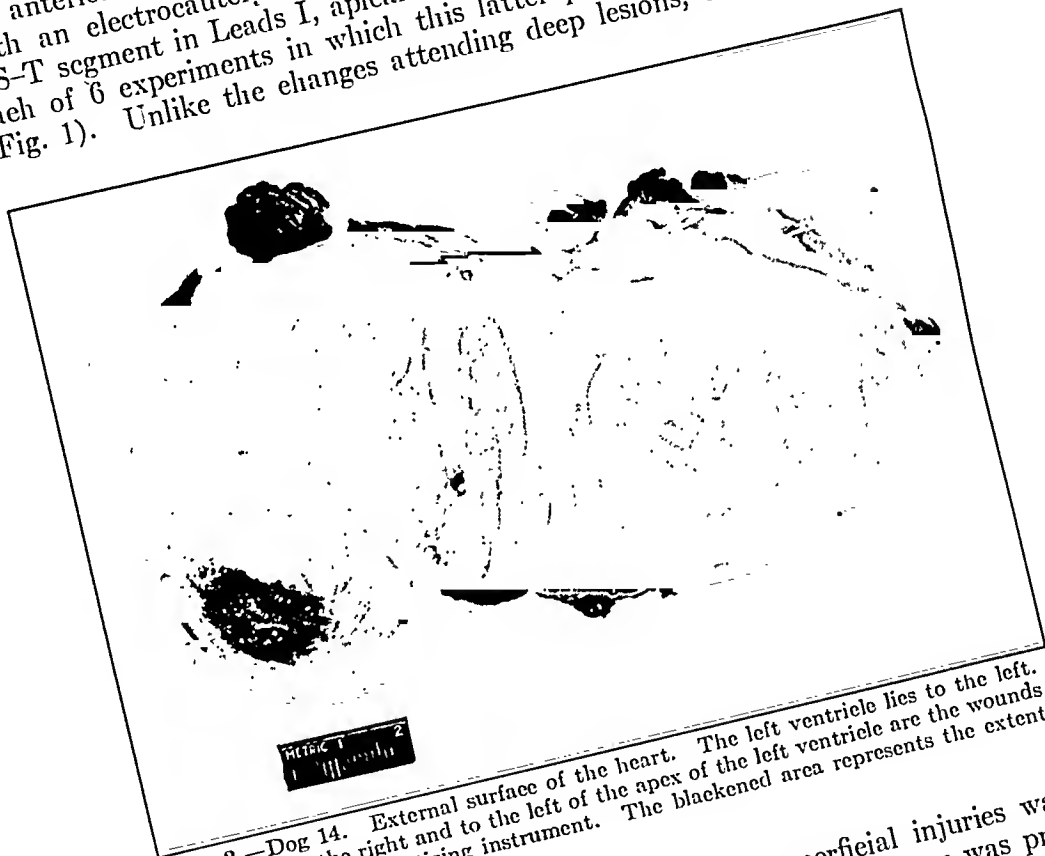


FIG. 2.—Dog 14. External surface of the heart. The left ventricle lies to the left. About 1 cm. to the right and to the left of the apex of the left ventricle are the wounds produced by the traumatizing instrument. The blackened area represents the extent of the burn.

elevation which followed the production of superficial injuries was maximal in the ECG's taken immediately after the injury was produced. Within 1 hour, the level of the segment had returned to the iso-electric line.

Depression of the RS-T segment was also a relatively rare event. Only one really satisfactory example occurred in these 22 experiments. The phenomenon was seen in Leads II and III immediately after trauma and disappeared in 15 minutes.

*Changes in the Configuration of the T Wave.* These changes were inconstant after deep myocardial injuries.

The most significant alterations seemed to be partial, complete or increased inversion of the T wave in the apical IV-R lead. This

change occurred in 13 of 22 experiments. In the remaining 9 experiments the form of this portion of the ECG was unchanged.

Deep inversion of the T waves in Leads II and III occurred in those 2 instances in which the QRS complexes in these leads were increased in height and width.

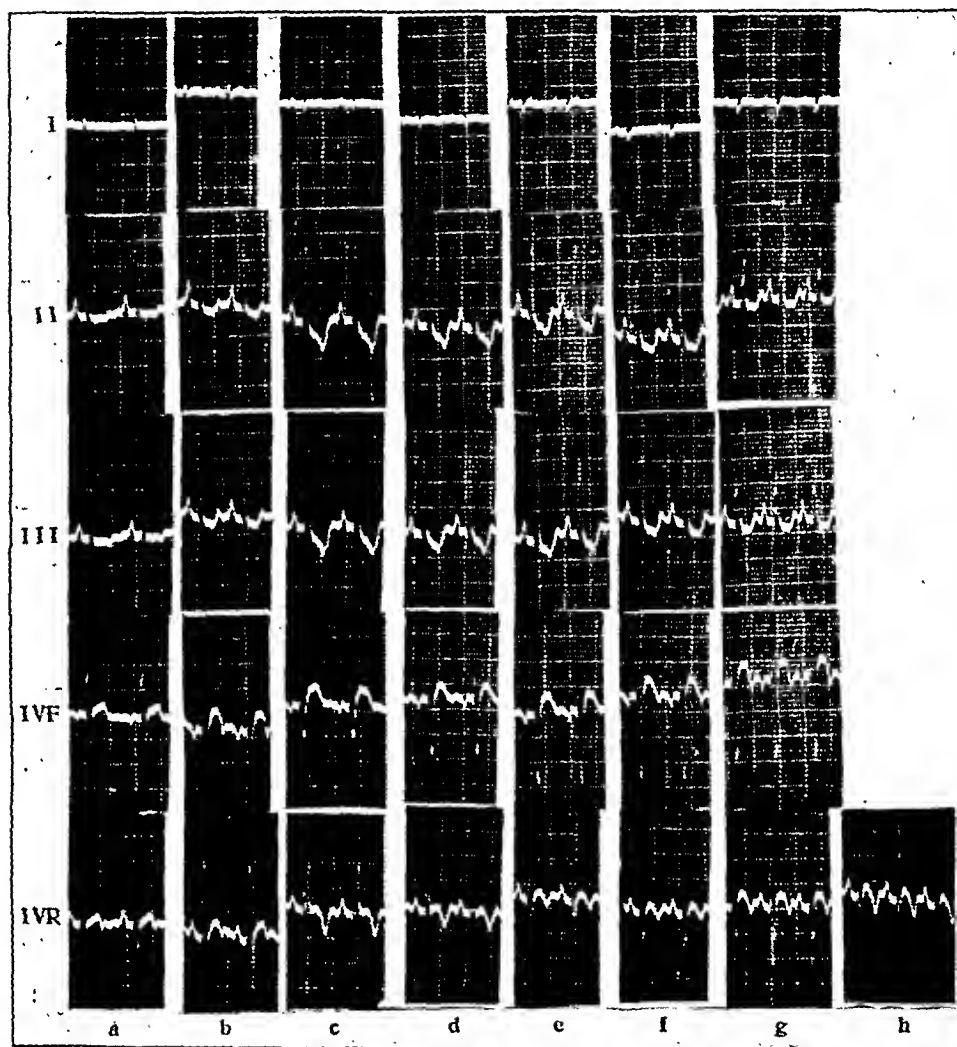


FIG. 3.—Dog. 13. Roman numerals and capital letters represent the leads. *a*, Control after anesthesia; *b*, control after opening chest and pericardium; *c*, 11 A.M., immediately after the first attempt at deep trauma *via* apex anteriorly; the entire lesion was produced at this one attempt; relatively little bleeding ensued; *d*, 12 noon, 1 hr. after the first attempt at deep trauma; *e*, 12:45 P.M., 1 hr. 45 min. after the first attempt at deep trauma; *f*, 1:40 P.M., 2 hrs. 40 min. after the first attempt at deep trauma; *g*, 4:30 P.M., 5 hrs. 30 min. after the first attempt at deep trauma; *h*, 4:30 P.M., an additional precordial lead in which the exploring electrode was placed 5 cm. to the left of the sternum in the fifth interspace ( $CR_5$ ).

**Comment.** Our results would seem to afford adequate support of the observation that damage to the endocardium and deeper layers of the myocardium of the apical portion of the left ventricle in dogs is

attended by certain changes in the configuration of the QRS complex in a precordial lead designated apical IV-R. Most constant among these changes was reduction in the height of the R wave. The development of a Q wave or of a notch low on the upstroke of the R wave were alternative types of change.

The significance of these observations rests on certain other findings, as follows: (1) An R wave of relatively high voltage was present in all control tracings of the apical IV-R lead. (2) A Q wave was never present in such control ECG's. (3) In control procedures in which a needle was introduced into the left ventricular cavity but no further



FIG. 4.—Dog 13. Interior of left ventricle. The lesion involves the base of both papillary muscles and the apical portion of the septum.

damage was inflicted, no significant changes occurred in the QRS complex even after several hours had passed (Fig. 5). (4) In those experiments in which the epicardium of the left ventricular apex was burned before production of a deep lesion, the height of the R wave was not altered appreciably.

Reference already has been made to the observation of Wilson and associates<sup>11,13</sup> that in direct leads from regions in which the inner layers of muscle were dead or had been replaced by scar tissue and in which the outer layers were still living and responding to the excitatory process, the QRS group was characterized by specific changes in that portion preceding and including the intrinsic deflection, while the

RS-T segment was not displaced. Limitation of space makes it impracticable to review the theory of Wilson in explanation of the

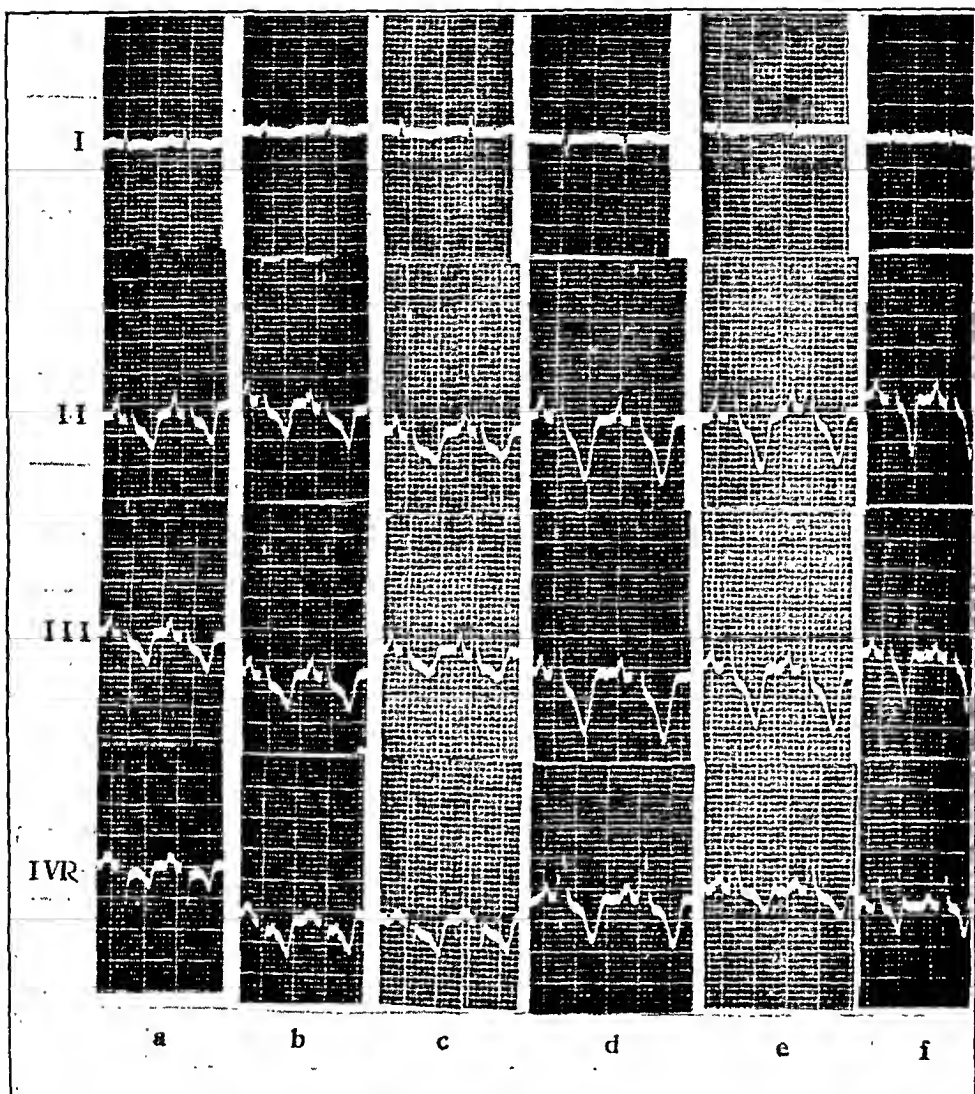


FIG. 5.—Dog 7. Roman numerals and capital letters represent the leads. *a*, 9:30 A.M., control after opening chest and pericardium; *b*, 9:38 A.M., after puncturing the left ventricular cavity *via* the apex anterior with a No. 18 Luer needle, shaking the heart for 1 min., withdrawing 2 cc. of blood and injecting the latter into the anterior surface of the left ventricle just to the left of the interventricular septum; *c*, 12:30 P.M., 2 hrs. 52 min. after control procedures; *d*, 1 P.M., 5 min. after the first attempt at deep trauma *via* apex anteriorly; the lesion was widespread, being deepest in the area just anterior to the anterior papillary muscle and in the apical portion of the septum; the base of the anterior papillary muscle also was damaged and the endocardium was stripped from the base of the posterior papillary muscle; *e*, 1:25 P.M., 30 min. after the first attempt at deep trauma; *f*, 4:25 P.M., 3 hrs. 30 min. after the first attempt at deep trauma.

peculiarities of this curve. The results obtained by him and his associates resemble those here reported in that in both it is the QRS com-

plex in which the characteristic changes occur, and, in both, the intrinsic deflection is reduced in magnitude but not completely obliterated.

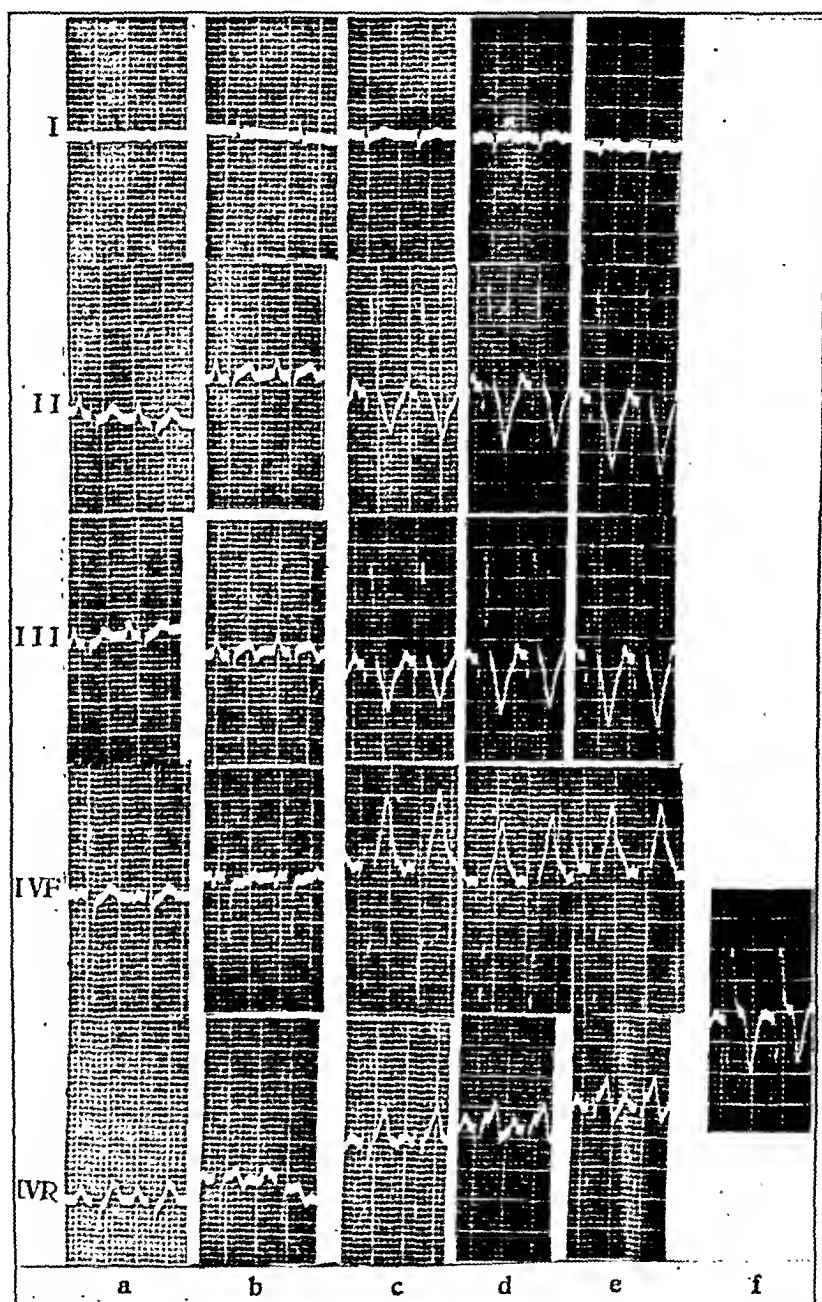


FIG. 6.—Dog 2. Roman numerals and capital letters represent the leads. *a*, Control after anesthesia; *b*, 9:20 A.M., control after opening chest and pericardium; *c*, 9:45 A.M., 10 min. after the first attempt at deep trauma; practically the entire endocardium was removed from the apical two-thirds of the left ventricular cavity (Fig. 7); *d*, 10:30 A.M., 55 min. after the first attempt at deep trauma; *e*, 3:45 P.M., 6 hrs. 10 min. after the first attempt at deep trauma; *f*, 3:45 P.M., exploring electrode 2 cm. to left of left sternal border in the fifth interspace.

The final solution of the source of these changes in the QRS complex must await further developments in the experimental field. They may originate from (1) injury to or destruction of the myocardial fibers underlying the endocardium or (2) damage to Purkinje's network or to the major subdivisions of the left branch of the bundle of His.

A study of the effects of damage of the endocardium and subendocardial myocardium on the width of the QRS complex leads to certain conclusions that appear to be significant. In each of the 22 experiments, there was extensive destruction of those tissues in which portions of Purkinje's system are supposed to lie. In spite of this fact, the width of the QRS complex remained unaltered in 20 experiments. The speed at which the excitatory impulse was propagated remained.



FIG. 7.—Dog 2. Interior of the left ventricle. The lesion extends almost to the free end of both papillary muscles and involves a major portion of the septum.

essentially unchanged, even though the course, as indicated by the form of the QRS complex, was altered. An increase in width of the QRS complex occurred only when the lesion involved an area high on the interventricular septum.

Only a few disconcerting exceptions restrain us from making the generalization that injury to the deeper layers of the myocardium has no appreciable effect on the level of the RS-T segment. We already have indicated our inability to explain these exceptions satisfactorily.

Certainly our results, as shown by the tracings reproduced in Figure 1, indicate that surface lesions exert a dominant influence on the level of the RS-T segment. In the apical IV-R lead, only minimal segmental changes followed the production of extensive deep

myocardial damage, while marked elevation of the RS-T segment occurred when a small superficial burn was made on a portion of the apex overlying the area of deep injury.

Wilson and associates have shown that the ECG effects of damaging deep muscle fibers with a sharp electrode are similar to the consequences of injuring superficial fibers if in each case the electrode is in contact with the damaged cells. If currents of injury are set up when fibers deep in the myocardium are damaged, why are the ECG effects of such currents, that is, elevation of the RS-T segment, so infrequently encountered when semidirect or indirect leads are used? A rather reasonable assumption seems to be that these currents of injury set up in the deep fibers are masked by the normal action currents arising in the uninjured superficial fibers in response to the excitatory process.

As a tentative explanation for the peculiarities of the curves recorded in these experiments in which significant injury was confined largely to the deeper layers of the myocardium, the following hypothesis is proposed: As the wave of excitation spreads from a point high on the septum into the myocardium of the left ventricle, the potentials recorded in the QRS complex are developed. The excitatory process has activated only the deeper layers of the heart when the first part of the QRS complex is inscribed. Hence lesions of the subendocardial myocardium produce changes in this part of the ECG, exhibited without inhibition because of the absence of potential changes in the more superficial layers.

The RS-T segment is inscribed during a period when both endocardial and epicardial regions of the myocardium are involved in the repolarization process. Because of the proximity of the uninjured superficial fibers to the surrounding conductile tissues, the electrical potentials developed here dominate this portion of the ECG, obscuring the effects of any injury potentials developed in the deeper layers of the myocardium. Consequently the RS-T segment has a fairly normal configuration in cases of injury confined to the deeper layers.

Because the process of repolarization may be prolonged in fibers of the injured areas, alterations in the direction of the terminal deflection (T wave) sometimes develop.

Much could be said about the part which unidentified surface injuries may have played in the production of the ECG changes which we have attributed to injury of the deeper layers of the myocardium. This issue was kept in mind throughout these experiments. Two observations are pertinent: (1) The ECG changes which we have ascribed to deep injury differ in kind rather than in degree from those which we and others have related to purely superficial damage, (2) Secondary injuries to surface areas overlying the sites of deep lesions were attended by the development of ECG patterns characterized by the presence of definite segmental elevation, a change which has been ascribed to the effects of trauma on epicardial fibers that are alive and respond to the excitatory process.

**Summary and Conclusions.** Myocardial injuries were produced in dogs by mechanical means. Damage to the endocardium and deeper layers of the myocardium of the apical portion of the left ventricle was attended by certain changes in the configuration of the QRS complex in a precordial lead designated apical IV-R. Most constant among these changes was a reduction in the height of the R wave. The development of a Q wave or a notch low on the upstroke of the R wave were alternative types of change.

These changes in the QRS complex might be derived from: (1) Injury to, or destruction of, the myocardial fibers adjacent to the endocardium; or (2) damage to Purkinje's network or the larger subdivisions of the left branch of the bundle of His.

Although in each of the 22 experiments under analysis there was accomplished an extensive destruction of those tissues in which portions of Purkinje's system are supposed to lie, in 20 experiments the width of the QRS complex remained unchanged. The speed at which the excitatory impulse was propagated apparently remained essentially unchanged, even though its course, as indicated by the form of the QRS complex, was altered. Also, a lesion high on the septum apparently not only is attended by a widening of the QRS complex but also it is the only lesion likely to produce this effect.

Our results indicate that surface lesions exert a dominant influence on the level of the RS-T segment. We have suggested that this circumstance may prevail not because the traumatized subendocardial fibers fail to produce currents of injury, but because the resulting injury potentials are masked by the normal action currents arising in the uninjured superficial fibers in response to the excitatory process.

Changes in the T wave following injuries to the deeper layers of the myocardium were inconstant. The most frequently recurring alteration was an inversion of the T wave in a lead designated apical IV-R.

#### REFERENCES

1. BETLACH, C. J.: *J. Pharm. and Exp. Ther.*, **61**, 329, 1937.
2. BOYD, L. J., and SCHERF, D.: *Bull. New York Med. Coll., Flower and Fifth Ave. Hosp.*, **3**, 1, 1940.
3. HILL, I. G. W., FRANKLIN, M. B., JOHNSTON, F. D., and WILSON, F. N.: *Am. Heart J.*, **16**, 309, 1938.
4. JOHNSTON, F. D., HILL, I. G. W., and WILSON, F. N.: *Am. Heart J.*, **10**, 889, 1935.
5. KISCH, B., NAHUM, L. H., and HOFF, H. E.: *Am. Heart J.*, **20**, 174, 1940.
6. MASTER, A. M., GUBNER, R., DACK, S., and JAFFE, H. L.: *Arch. Int. Med.*, **67**, 647, 1941.
7. ROBB, J. S., and ROBB, R. C.: *AM. J. MED. SCI.*, **197**, 7, 1939.
8. ROBB, J. S., and ROBB, R. C.: *AM. J. MED. SCI.*, **197**, 18, 1939.
9. WILSON, F. N., HILL, I. G. W., and JOHNSTON, F. D.: *Am. Heart J.*, **9**, 596, 1934.
10. WILSON, F. N., HILL, I. G. W., and JOHNSTON, F. D.: *Am. Heart J.*, **10**, 163, 1934.
11. WILSON, F. N., HILL, I. G. W., and JOHNSTON, F. D.: *Am. Heart J.*, **10**, 903, 1935.
12. WILSON, F. N., JOHNSTON, F. D., and HILL, I. G. W.: *Am. Heart J.*, **10**, 176, 1934.
13. WILSON, F. N., JOHNSTON, F. D., and HILL, I. G. W.: *Am. Heart J.*, **10**, 1025, 1935.



# PROGRESS OF MEDICAL SCIENCE

## MEDICINE

UNDER THE CHARGE OF  
JOHN H. MUSSER, M.D.

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS

---

### BRONCHIAL ASTHMA: SOME PROBLEMS IN DIFFERENTIAL DIAGNOSIS

By W. A. SODEMAN, M.D.

DEPARTMENT OF PREVENTIVE MEDICINE, TULANE UNIVERSITY OF LOUISIANA  
NEW ORLEANS, LA.

ALTHOUGH the word *asthma* is derived from a Greek expression meaning panting, it has come to represent dyspnea associated with wheezing. It is loosely used to refer to the disease *bronchial asthma*, yet almost all diseases of the lungs, as well as some involving organs lying outside the lungs, may give the symptom asthma, that is wheezing and dyspnea. Rackemann<sup>38a</sup> lists the causes for this symptom as (1) spasm and edema of the bronchial mucous membrane, (2) exudates in the tubes, (3) obstruction by foreign body or tumor, (4) emphysema, and (5) congestive heart failure. Some of the ways in which the word *asthma* has been used are listed by Dorland<sup>12</sup> as follows: cardiac asthma (certain instances of left ventricular failure), Elsner's asthma (angina pectoris), Kopp's, or Wichmann's asthma (thymic dyspnea), steamfitters' asthma (asbestosis) and stone asthma (dyspnea associated with bronchial calculus). Certainly the problem of the differentiation of the diseases producing asthma is primarily that of differentiation of the causes of dyspnea with noisy respirations. Wheezing may be manifested only by sonorous and sibilant râles heard on auscultation so that these findings enter into the differential diagnosis.

The cardinal syndrome producing asthmatic breathing is bronchial asthma, characterized by recurrent attacks of dyspnea which is more marked in expiration and accompanied by wheezing and cough. These episodes result from narrowing of the bronchial lumina from edema of the bronchial mucosa, secretion of a thick exudate into the bronchi, and bronchial muscular spasm from stimuli which, in most individuals, cause no such reactions. The process is usually, in great part at least, a reversible one so that the disease is manifested by episodes of dyspnea. Pathologic findings include the presence of mucinous plugs, an eosinophilic infiltration into the bronchial mucous membrane, hyaline thickening of the basement membrane of the bronchus and hypertrophy of the musculature.<sup>48</sup> Cohen,<sup>8</sup> comparing the reaction to those resulting from experimental histamine injections,<sup>24</sup> described it as exhibiting a characteristic inflammatory reaction. In this light bronchial asthma is a specific and

unusual type of bronchial inflammation generally not infectious in origin and readily reversible. It is a *peculiar* type of bronchitis, which accounts for the difficulty in its differentiation at times from bronchitis of the usual infectious inflammatory type, a reaction not so readily and quickly reversible. Such infection, however, if effecting sufficient narrowing of the lumen, may produce wheezing and dyspnea as does bronchial asthma, as may foreign body in the bronchus, bronchial carcinoma and other diseases for which the treatment is radically different from that of bronchial asthma.

In the diagnosis of bronchial asthma the most important single factor is usually the history. There may be a past or family history of allergic manifestations. Attacks are frequent at night. Certain prodromes may occur, such as plugging of the nose, sneezing, rhinorrhea, burning or heaviness in the chest, gastro-intestinal disturbances, such as heaviness or diarrhea, as well as diuresis, itching and urticaria. The paroxysm gradually reaches its height and, if severe, a sensation of suffocation is experienced. The respiratory rate may go up but frequently respirations are slow and labored. Accessory respiratory muscles are brought into play; the pulse rate is elevated and cyanosis may appear. The jugular and supraclavicular regions, intercostal spaces and epigastrium retract with inspiration. The patient generally complains of difficulty in getting air out, or will do so if asked to analyze his difficulty. Expiration is prolonged, accompanied by an effort, and aided by a contraction of the abdominal muscles. Wheezing is usually associated with expiration and often inspiration as well, and may be loud enough to be heard by bystanders. Cough may occur at or near the termination of the episode. There are small amounts of tenacious sputum containing white masses of mucus. Coëxistent bronchial disease may modify the sputum. Examination of the sputum usually shows many eosinophils and at times Charcot-Leyden crystals, Curschmann's spirals and even bronchial casts. The patient invariably sits up during an attack. Examination of the chest shows bilateral sonorous and sibilant râles, especially on expiration. Expiration is prolonged. There is increased resonance to percussion. Cyanosis may be seen. The attack may last for hours or days and in the recovery period the auscultatory squeaks and groans remain. The episode may be arrested at any stage. If arrested at the beginning, when symptoms are limited to some difficulty in deep breathing, a feeling of oppression, chest constriction and tightness, bronchial asthma may not be diagnosed. The patient may go on with such subjective sensations for a considerable period of time before episodes advance to a stage in which sonorous and sibilant râles suggest the diagnosis. The sense of constriction and the mild dyspnea may lead the patient to suspect heart disease or bronchial disease other than asthma. If arrested after the appearance of sonorous and sibilant râles, but before the attack progresses to its peak, the episode may be confused with other conditions itemized below, particularly the bronchial syndromes.

The patient usually presents himself with the above story of paroxysmal attacks of dyspnea, usually with wheezing and cough. Such episodes may have been frequent or rare, and long or short in duration. Hay fever or other known allergic manifestations may have been present. The diagnosis then may be simple and easy, and usually is. Yet errors in diagnosis are extremely important for, as already stated, the therapy of conditions simulating bronchial asthma is usually entirely different and at times the condition is a correctable one which, when treated, disappears. If the patient has had only one attack, the diagnosis is likely to be in

more doubt and further observation may be necessary. The patient may present himself for examination between attacks, and, when there is doubt about the diagnosis, a complete examination is necessary, including investigation of the blood and urine, chest roentgenogram, a complete cardiac work-up and, at times, even laryngoscopy and bronchoscopy.

Commonly grouped with those diagnosed as asthmatics are other patients not giving the classic picture sketched above. These patients usually do not have an onset early in life, a family or past history of allergic manifestations, positive skin tests or environmental control.<sup>8</sup> Onset of asthmatic breathing is usually in middle age, often preceded by months or years of spasmodic cough. Infections of the nose, throat, or bronchial tree may have accompanied the episodes of cough and bronchitis. Age usually helps to differentiate these patients but not always. Such asthmatic episodes may occur in children without family or past histories of allergy and may follow whooping cough, measles, or other respiratory infection. Such children have a gradual onset of attacks and may not be well in the intervals.<sup>33</sup> The term *infective asthma*, or *asthmatic bronchitis*, is often applied to this picture. However, these episodes are much commoner beyond the age of 40 and in some of the patients causative factors leading to the asthmatic episodes are not at all well established<sup>38c</sup> even though chest infection, paranasal disease and many other factors are sought. Past and family histories of allergy are only occasionally elicited; allergens as a cause are rarely found, and response to anti-allergic treatment may be poor.<sup>1</sup> As Alexander pointed out, the symptoms may start with a cough and mucoid sputum, which may last for weeks, with a few musical râles. Recovery may occur with later repetition, often with frank wheezing. With repeated episodes response to iodides and epinephrine may become less dramatic. Cough, at times with wheezing, may persist between the episodes, which become less clear-cut in onset or disappearance. More inspiratory distress is often evident. The lack of seasonal variations, environmental control, histories of allergy and positive skin tests has led to the belief that these patients have within themselves the cause of their asthmatic episodes. The term *intrinsic asthma* is applied in contradistinction to extrinsic, or typical bronchial asthma in which the causative factor arises in the environment. Rackemann<sup>38b</sup> has been particularly interested in this group. He has found no satisfactory theory to explain these cases but does divide them into 3 groups: (1) a picture closely related to acute respiratory infection, the disappearance of which is followed by a receding of the asthmatic symptoms, which recur with a repetition of the infection, and which is termed *asthmatic bronchitis*; (2) a group with no relationship to season, environment, or diet, with no known allergic relationships; and (3) patients with evidence of emphysema, bronchiectasis or heart disease with asthma as a result of bronchial exudate, spasm, or edema, occurring as a part of the primary disease.

As already stated, the history and clinical picture of bronchial asthma may be so characteristic that the diagnosis is easily made, often by the patient before he sees the physician. But occasions arise when there is confusion with other diseases or when other diseases may be mistaken for bronchial asthma. The presence of other disease may overshadow the asthmatic picture<sup>23</sup> or *vice versa*. The great and important differences in treatment and prognosis of many of these conditions demand that they be ruled out. Maytum<sup>30a</sup> has listed these conditions according to systems and his table is reproduced here (Table 1). With this array of con-

ditions producing dyspnea and simulating asthma, it is obvious that the great differences in treatment demand adequate differentiation.

TABLE 1.—MAYTUM'S LIST OF CONDITIONS THAT MAY SIMULATE ASTHMA

**A. Respiratory System.**

**I. LARYNX.**

1. Laryngeal spasm:
  - a. Spasmodic croup
  - b. Laryngismus stridulus
  - c. Laryngeal crisis of tabes dorsalis
2. Inflammation:
  - a. Acute (acute laryngitis, diphtheritic laryngitis)
  - b. Chronic (tuberculosis, syphilis)
3. Angioneurotic edema
4. Paralysis of the vocal cord
5. Laryngeal stenosis
6. Foreign body
7. Neoplasm:
  - a. Benign
  - b. Malignant

**II. TRACHEA AND BRONCHI.**

1. Intrinsic lesions:
  - a. Acute and chronic bronchitis
  - b. Chronic inflammation with stenosis (bronchiectasis, tuberculosis, syphilis, foreign body)
  - c. Neoplasm (benign; malignant)
2. Extrinsic lesions:
  - a. Substernal enlargement or carcinoma of the thyroid gland
  - b. Enlargement of the thymus gland
  - c. Aneurysm of thoracic aorta
  - d. Tuberculous tracheobronchial nodes
  - e. Mediastinal neoplasm (benign; malignant)

**III. LUNG.**

1. Inflammation:
  - a. Pneumonia
  - b. Tuberculosis
  - c. Pneumoconiosis and pulmonary fibrosis
2. Idiopathic pulmonary emphysema
3. Neoplasm of lung and pleura
4. External pressure:
  - a. Pneumothorax
  - b. Hydrothorax

**B. Circulatory System.**

**I. CARDIAC DECOMPENSATION**

**II. CORONARY SCLEROSIS**

**III. PAROXYSMAL AURICULAR FLUTTER OR FIBRILLATION; PAROXYSMAL TACHYCARDIA**

**C. Renal System (manifested in circulatory system).**

**D. Nervous System.**

**I. FUNCTIONAL AIR HUNGER**

**II. HYSTERICAL POLYPNEA**

**III. RESPIRATORY SYNDROME FOLLOWING ENCEPHALITIS**

Difficulty in breathing associated with some type of noisy respiration accounts for the confusion of most of these conditions with bronchial asthma. This is true with *laryngeal disease*. The dyspnea of laryngeal obstruction is characterized by retraction on inspiration of the area of the suprasternal notch and at times the ribs, supraclavicular and epigastric regions as well. This, with inspiratory stridor is a distinctly inspiratory disturbance. If any doubt arises, direct laryngoscopy will settle the

diagnosis. Such findings as these may occur in the child with congenital deformities of the larynx, laryngeal or tracheal stenosis, or both, as seen after high tracheotomy, trauma, diphtheria, or surgical infections, and in laryngeal spasm. Spasm is occasionally a part of the picture of spasmophilia, evidences for which (Chvostek's sign, electrical excitability, changed blood calcium levels) may be sought. Spasmophilia in children with asthma-like episodes was described by Lederer<sup>26</sup> as *bronchotetany*. Neoplasm, foreign body, paralysis of the vocal cords and edema of the larynx give similar pictures, with hoarseness, croupiness, at times with special characteristics peculiar to each such as history of foreign body or evidences of angioneurotic edema. Acute inflammations are likely to be accompanied by tracheitis and other evidences of inflammation, including systemic findings. Inspection of the laryngeal cavity should be done when doubt exists. Retropharyngeal abscess may produce similar symptoms and should be diagnosed by the local examination.

*Bronchial disease* of many types simulates bronchial asthma. Foreign body in the bronchus may produce wheezing respiration which is mistaken for bronchial asthma, especially if a history of foreign body is not evident. Jackson<sup>21</sup> stressed the *asthmatoïd wheeze*, a dry wheezing sound heard with the ear close to the open mouth during expiration. Foreign body in the stem bronchus is likely to show unilateral physical findings, a most important differential point, and roentgenologic evidences may be present even if the foreign body is not radiopaque. Intracheal foreign body may produce a snapping sound heard at the mouth when the patient coughs and a thud may be felt in the subglottic area over the trachea. Tracheobronchial stenosis of any type may be mistaken for asthma. Stridor, localization of findings, and bronchoscopy will make the diagnosis.

Acute infectious laryngotracheobronchitis in children produces stridor and an ashen gray color with a croupy cough, signs of laryngeal and bronchial obstruction and a febrile response. Gummy ropy secretions are present and require bronchoscopy for removal. Neoplasm of the bronchus also may produce noisy respiration and dyspnea.<sup>25</sup> Here again the history, physical and roentgenologic findings should suggest the diagnosis and bronchoscopy should, if necessary, be employed to establish a diagnosis. Benign tumors, as well as bronchogenic carcinoma, may be mistaken for bronchial asthma. Shortness of the duration, and localization of findings to one side should lead to roentgenologic and bronchographic studies, if necessary. Benign tumors are likely to give a longer history than the malignant type, and thus may simulate bronchial asthma more closely.

Bronchogenic tumors are among the many conditions which simulate bronchial asthma and which are diagnosed only by careful study. Bronchoscopy is particularly indicated when such tumors appear as possible causes for the picture. Clerf<sup>7</sup> and Friedberg<sup>15</sup> have pointed out these problems very clearly. They have shown that the bronchi elongate and expand in inspiration and contract and shorten in expiration. For this reason pathologic processes which narrow, or partially block, the bronchial lumina will interfere especially with the outflow of air. Friedberg reaffirms the statement that endoscopy is warranted in any case of "atypical bronchial asthma" which does not respond readily to diagnosis and therapy.

Prickman and Moersch<sup>37</sup> have pointed out certain instances when bronchoscopy is extremely helpful in the diagnosis of bronchial asthma, such as in the occasional case of bronchostenosis which they feel is a more

common complication of both allergic and so-called infectious asthma than is generally believed. They have found definite localized stricture-like narrowing of a bronchus, or bronchi, in certain instances with impaired flow of air beyond the stricture and retention of secretions and even partial or complete atelectasis. These findings were present in 60 of 140 patients with asthmatic episodes who were specially selected for bronchoscopy. Certain clinical findings, characteristic symptoms, and physical and roentgenologic observations may lead to the suspicion of bronchostenosis. Severe persistent and sometimes paroxysmal cough which aggravates the asthma is such a symptom. There is difficulty in raising the sputum even with severe cough only to have a profuse sputum later. The sputum is mucopurulent and, in 40% of Prickman and Moersch's patients, at some time blood streaked. Febrile episodes, either with or without chills occurred in 68% of their cases. It was usually moderate and lasted several to many days, to be followed by an increase in sputum on its subsidence. Leukocytosis was usual.

The above history, or parts of it, should arouse suspicion of bronchostenosis or some other complication. Likewise, 53% of Prickman and Moersch's series gave a history of pneumonia, and 35% a history of pleurisy. Bronchostenosis was frequently mistaken for bronchopneumonia because of fever, cough and purulent blood-tinged sputum, and evidence of atelectasis. Repeated episodes of pneumonia with asthma should lead to suspicion of bronchostenosis and to bronchoscopy. It is only a small percentage of patients with asthma that need bronchoscopy and bronchostenosis should be added to the list of diseases which, when suspected, are to be ruled in or out by this means.

In children with acute tracheal and bronchial inflammation, wheezing may develop and the chest sounds "asthmatic." Simple infection without allergic background may cause sufficient narrowing to produce these signs and the differentiation may be difficult unless the patient is studied for a period of time. This process starts slowly and ends gradually. There are no paroxysms and signs of infection are present. In older individuals with chronic bronchial disease, bronchitis, bronchiectasis, and emphysema, particularly with superimposed infection, dyspnea with wheezing may develop. To determine whether mechanical narrowing alone is the causative factor or whether bacterial hypersensitiveness also acts as an exciting factor becomes the problem, which has already been discussed. In patients with known bronchial asthma for long periods of time, especially those in whom chronic bronchitis has developed or in those with intrinsic asthma, attacks may become refractory to treatment, the so-called *status asthmaticus*. Fever and signs of infection may appear, often with purulent bronchitis and thick ropy secretions in the smaller bronchi or with peribronchial pneumonia. The recognition of such complications is important to proper therapy. Alexander<sup>1</sup> has pointed out the frequency of *status asthmaticus* and of marked eosinophilia in intrinsic asthma. At autopsy at times eosinophilic infiltrations have been found in the bone marrow and myocardium.<sup>5</sup>

The association of eosinophilia and periarteritis nodosa with asthmatic episodes is most interesting. Alexander<sup>1</sup> has called attention to its frequent presence in *status asthmaticus*. Harkavy<sup>17</sup> has also pointed out its occurrence and Rackemann and Mallory<sup>39</sup> found in a series of 50 cases of fatal asthma 5 with periarteritis nodosa, a high figure for the incidence of this disease. Lichtman and his associates<sup>28</sup> noted the fact that asthma is said to occur early in about 15 to 20% of the cases of periarteritis nodosa

and eosinophilia may reach 70 to 80%, a finding which may be a clue to its diagnosis.

Some evidence to indicate a possible relationship of periarteritis nodosa to allergic phenomena rests in a report of Rieh<sup>40</sup> in which he records the observation of periarteritis nodosa in patients dying of acute infection when serum sickness was also present. He indicated that vascular lesions of this type can be a manifestation of the anaphylactic type of hypersensitivity. In a report with Gregory<sup>41</sup> he presented experimental evidence of the disease in rabbits which had been treated with foreign protein. Later Selye and Pentz<sup>42</sup> by chronic severe overdosage with desoxycortosterone acetate produced in animals lesions similar to those of periarteritis nodosa. It would appear that periarteritis nodosa is not a disease entity itself, and although its etiology is not definitely established, a relationship to allergic phenomena is very possible.

Involvement of the *lungs* with disease which produces dyspnea, especially if noisy respirations of one type or another occur, is often confused with bronchial asthma. Lamson, Butt and Stickler's<sup>25</sup> autopsy series of a group of patients with asthma includes many of these conditions, such as carcinoma, pneumoconiosis and tuberculosis. Pulmonary emphysema is most difficult to differentiate at times. History may be most important, for typical bronchial asthma often produces emphysema. The dyspnea of emphysema may occur in paroxysms during infection but most often develops slowly over long periods of time; effort is definitely a precipitating factor producing wheezing respirations. Foreign bodies in the bronchi causing pneumonitis have already been mentioned. In pneumoconiosis paroxysms of dyspnea are not clear-cut and historical data leading up to the development of the picture are most helpful. Roentgenograms of the chest are important. Roentgen ray and radium therapy to the chest may produce asthma-like dyspnea. Hydatid cysts may produce asthmatic breathing and eosinophilia and urticaria may be present. Asthmatic dyspnea has been described as the sole presenting symptom of generalized endolymphatic carcinomatosis,<sup>31</sup> in which metastases are found to the pulmonary lymphatics and in which the Roentgen picture is a pattern of thin lines often with reticulation extending from the hilum toward the periphery. Actual nodules may not be present and the picture may simulate that of pneumoconiosis, miliary tuberculosis, lymphoma or fibrosis resulting from infections.

It is to be remembered that bronchial asthma may be the underlying cause of certain pulmonary changes.<sup>9,32,35</sup> Edema and spasm of the bronchi, together with mucinous plugs, are known to produce areas of atelectasis and even massive collapse of the lung<sup>36</sup> with relief by bronchoscopy. In 1935, H. Miller and his associates<sup>32</sup> described a group of 11 allergic children with *allergic bronchopneumonia*, changes in the lung which they felt resulted from bronchial obstruction, allergic reactions of the lung parenchyma, or both. Frequently changing physical and Roentgen signs characterized the pictures. Fever occurred. Common diagnoses on these patients had been asthmatic bronchitis, recurrent bronchitis, bronchopneumonia, abortive bronchopneumonia, non-tuberculous pulmonary infection, tuberculosis, perifocal tuberculosis, bronchiectasis, pulmonary abscess and foreign body.

In 1932, Löffler described a syndrome of transient pulmonary infiltration with associated leukocytosis and eosinophilia found especially in allergic individuals. In 1936 he reported 51 cases.<sup>29</sup> Since then there have been numerous reports on this picture.<sup>14,16,20,22,42,45,51</sup> Hansen-Pruss

and Goodman<sup>16</sup> have summarized the features of this picture as: (1) occurrence in allergic people, (2) varying degrees of leukocytosis and eosinophilia, (3) afebrile course, (4) pulmonary consolidation, (5) persistent severe asthma, (6) lack of response to sulfa drugs, and (7) history of frequent respiratory disease. The generally benign nature of Löffler's cases contrasts with some of those described by Miller and his group.<sup>32</sup> The roentgenograms of the chest are especially important. Varying shadows of different sizes, shapes and location, either unilateral or bilateral, may on single films be indistinguishable from those seen in tuberculosis. Serial films may be necessary for differentiation. Eosinophilia does not parallel the chest infiltrations. Löffler felt that bronchial asthma with partial atelectasis, tuberculosis, pneumonia, and infarction were not part of the picture. He considered ascariasis a possible cause, and others since then have found worm infestations and amebiasis associated with the picture. A possible relationship of so-called tropical eosinophilia to these pictures must be considered.<sup>46</sup>

The relationship of tuberculosis to asthma has received much attention. Tuberculosis of the lungs may produce respiratory distress in many ways, through the pressure of tracheobronchial nodes, by fibrotic contraction or adhesions producing mediastinal shifts, mechanical embarrassment of the cardiovascular system, tracheal and bronchial compression or tugging and by bronchial strictures.<sup>52</sup> Tuberculous tracheobronchial nodes are most likely to cause compression in children especially before the 2nd year. Dyspnea may be exertional but is constant and does not respond to epinephrine. Tuberculin tests and roentgenographic studies will help in differentiation. Tuberculosis may also coexist with bronchial asthma and the latter may mask the former. There has been much controversy as to possible causal relationships when the two occur together (*tuberculo-allergic asthma*).<sup>50</sup> General views are that causal relationships between the two are either infrequent<sup>13,50</sup> or entirely absent. In 1 series<sup>50</sup> of 452 asthmatics pulmonary tuberculosis was present in 25 (5.5%). On the other hand some feel that tuberculosis is no more frequent in asthmatics than in the general population<sup>23</sup> and that tuberculosis plays no particular etiologic rôle in the production of the asthma, at least no more than other respiratory infections which render the mucosa vulnerable. In 1 series<sup>49</sup> the incidence of asthma among 386 patients with active tuberculosis was 3.1 %, a figure which approximates the reported incidence of asthma among the rest of the population. Sprague<sup>47</sup> believes that bronchial asthma and pulmonary tuberculosis appear as coexisting diseases much more frequently than either the literature or the experience of the general practitioner would show. There is a tendency to regard the asthmatic as "just another asthmatic." Each individual case, if studied, may reveal changes which cause the physician to suspect tuberculosis. Anorexia, unusual loss of weight, fever, change in character of cough, amount and type of expectoration, bloody sputum, sweats, tuberculosis contacts, elevated pulse rate, secondary anemia, physical findings other than those of typical asthma, should lead to Roentgen ray studies. The entire problem of tuberculosis and asthma has been reviewed by Tocker and Davidson.<sup>49</sup> One must be alert to this complication.

*Intrathoracic disease* of other types may simulate bronchial asthma. Tumors of the mediastinum, substernal goiter, inflammatory disease, mediastinal abscess, Boeck's sarcoid,<sup>3</sup> enlargement of the peribronchial or mediastinal lymph nodes, as in Hodgkin's disease, and aneurysm of the aorta must be considered. The dyspnea ascribed to thymic enlarge-



ment accompanies other manifestations of that picture. In aneurysm and mediastinal tumors, for example, attacks may be paroxysmal. Other evidences of disease than asthmatic breathing, for example stridor, hemoptysis, signs of mediastinal pressure, should be sought, but differentiation may require roentgenograms and even bronchoscopy, as well as history and physical examination.

*Cardiac asthma* is one of the manifestations of left ventricular failure and is often called paroxysmal nocturnal dyspnea. It simulates bronchial asthma in some respects, at times very closely, and is one of the most important differentiations in older patients. Although cardiac asthma, like bronchial asthma may come on during the day, it is most common, again like bronchial asthma, at night. The dyspnea may simulate very closely that of bronchial asthma, but respirations are often more rapid and on occasion the frothy pink sputum of pulmonary edema is present. Chest findings may be those of typical bronchial asthma and differentiation is then difficult. Moist basal râles may be present, alone or with sonorous and sibilant râles. Occasionally nothing abnormal is heard on auscultation. Other evidences of heart disease, enlargement of the heart, significant murmurs, precordial pain, evidences of heart failure in the past or at present, edema, may occur but at times it may be impossible to distinguish bronchial from cardiac asthma on history and physical grounds unless the patient is followed for some time. Sputum studies for eosinophils and determinations of the circulation time are helpful.

The circulation time, especially from arm to tongue, has been studied extensively in cardiac failure and to some extent in bronchial asthma. The findings of Hitzig, King and Fishberg<sup>19</sup> in 1935 of an arm-to-tongue time ranging from 18 to 60 or more seconds in cardiac failure have been amply confirmed. Occasionally exceptions are found and such patients occasionally have a normal circulation time. In bronchial asthma the time has been reported as not prolonged or even as accelerated.<sup>4</sup> Cottrell and Cuddie,<sup>11</sup> using decholin, found the arm-to-tongue time in bronchial asthma to vary from 10 to 15 seconds. The figures were normal both during attacks and in the intervals between asthmatic episodes.

Cardiac asthma is most common in the older patient, especially beyond the age of 50, a time when bronchial asthma is less likely to have its onset, only about 15% starting in the 5th and 6th decades. Eosinophilia in the blood and sputum favors bronchial asthma, but occurs in other diseases and when heart disease is a complication of bronchial asthma. Physical examination of the lungs may show basal râles or pleural effusion which usually mean heart disease. Levine<sup>27</sup> stresses the presence of basal moist râles and the absence of diffuse sonorous and sibilant râles as a differential point. When present these findings are extremely helpful. The finding of evidences of heart disease producing strain upon the left ventricle, either by physical or roentgenologic examination, establishes the etiologic agent for cardiac asthma and favors heart disease as a cause of the picture. Elevated venous pressure, if present, falls in the same group. The absence of allergic manifestations, some already mentioned above, is also helpful. An attack of cardiac asthma may terminate after epinephrine has been given but not as uniformly as does bronchial asthma.

It must be remembered that heart disease may occur in the patient with bronchial asthma, either by coincidence or as the result of the bronchial asthma. That bronchial asthma may be important in the production of heart disease is debated. The general consensus is that heart disease from such cause is not common,<sup>2,10,25,35,43</sup> although the *cor pulmonale*

type of cardiac damage with right ventricular hypertrophy and even failure has been reported on this basis.<sup>10,43</sup> Harkavy and Romanoff<sup>18</sup> have reported electrocardiographic changes which are in large part not extensive and are reversible. Schiller, Colmes and Davis<sup>43</sup> found that cardiac changes resulting from chronic bronchial asthma are more common than is generally believed. Of 12 autopsied cases with bronchial asthma of 6 or more years' duration, 5 died in congestive heart failure and 4 of these showed predominant hypertrophy of the right ventricle. They pointed out that the diagnosis of circulatory failure in such patients is difficult because of dyspnea caused by emphysema. Some show no edema, and when it does occur, it may appear suddenly and progress rapidly.

Paroxysmal cardiac irregularities, especially auricular fibrillation and flutter and paroxysmal tachycardia, may produce episodes of dyspnea, but other characteristics, especially on examination of the patient, will easily differentiate them from bronchial asthma.

Disturbances outside the respiratory tract and the thoracic cage may be confused with bronchial asthma. This is true of sighing respiration and *hysterical respiratory distress*, both of which bear some superficial resemblances to bronchial asthma. Hysterical overbreathing, which may give symptoms of hyperventilation, is easily differentiated when the patient is seen in an attack. There may be a close association with emotional factors or fatigue. (This may occur at times with bronchial asthma.) Polypnea with rapid respirations, rather than the slow labored dyspnea of bronchial asthma, is present. There is no sputum; typical auscultatory findings are not present; attacks may be of short duration; and onset and offset of attacks are more abrupt than in bronchial asthma. When the patient is seen between episodes, some observers<sup>34</sup> have injected vagotonic drugs (meholyl) which are likely to precipitate attacks of bronchial asthma, for differentiation. Other evidences of hysteria should be sought as well.

The syndrome of *sighing respirations*<sup>5,30b</sup> may accompany hysteria or other psychoneuroses, but not necessarily so. Stable individuals under unusual circumstances may also present this picture. Episodes of difficulty in breathing occur and bronchial asthma may, therefore, be suspected. Occasional sighing respirations are common, especially in nervous and neurotic individuals. The patient feels that he or she cannot get air into the chest. In emotional upsets or during periods of mental stress and strain, such respirations are likely to be more frequent. Repeated persistent rapid "attacks" may occur. A feeling of pressure is often present and the patient places his hands over the chest to show its presence. Shallow respirations are followed by deep sighing respirations easily recognized when seen. If frequent and repeated, such sighing attracts the patient's attention. He feels distress, feels suffocation, and may want to get out into the air or open a window. He may become pale and perspire. While occurring often during the day, such attacks may appear at night and especially then is bronchial asthma suspected. Overbreathing may lower the alveolar carbon dioxide and thereby cause alkalosis. When the patient is seen in an attack the respiratory distress is easily recognized. Respirations are deep and sighing, similar to those occurring occasionally between attacks. The rate may not be rapid but accessory respiratory muscles may be used. There is no cough, wheezing or sputum. Symptoms of tetany may develop, such as lightheadedness, vertigo, paresthesias, tingling of the fingers and toes, precordial distress,

sense of constriction of the thorax and sometimes carpopedal spasm and spontaneous facial twitchings. These may be reproduced if the patient deliberately overbreathes for 15 to 20 respirations.

*Postencephalitic hyperpnea*<sup>33a</sup> may simulate bronchial asthma for it is accompanied by forced breathing. The breathholding and other associated postencephalitic findings will permit differentiation.

#### REFERENCES

- (1.) Alexander, H. L.: *Internat. Clin.*, 3, 226, 1941. (2.) Alexander, H. L., Luten, D., and Kountz, W. B.: *J. Am. Med. Assn.*, 88, 882, 1937. (3.) Benedict, E. B., and Castleman, B.: *New England J. Med.*, 224, 186, 1941. (4.) Bernstein, M., and Simpkins, S.: *Am. Heart J.*, 17, 218, 1939. (5.) Browning, W. H.: *South. Med. J.*, 35, 914, 1942. (6.) Chafee, F. H., Ross, J. R., and Gunn, E. M.: *Ann. Int. Med.*, 17, 45, 1942. (7.) Clerf, L. H.: *Ann. Int. Med.*, 9, 1050, 1936. (8.) Cohen, M. B.: *Ann. Int. Med.*, 20, 590, 1944. (9.) Cohen, S.: *New Orleans Med. and Surg. J.*, 94, 440, 1942. (10.) Colton, W. A., and Ziskin, T.: *J. Allergy*, 8, 347, 1937. (11.) Cottrell, J. D., and Cuddie, D. C.: *Brit. Med. J.*, 1, 70, 1942. (12.) Dorland, W. A.: *American Illustrated Medical Dictionary*, 19th ed., Philadelphia, Saunders, 1942. (13.) Fraenkel, E. M.: *Brit. Med. J.*, 2, 513, 1934. (14.) Freund, R., and Samuelson, S.: *Arch. Int. Med.*, 66, 1215, 1940. (15.) Friedberg, S. A.: *J. Am. Med. Assn.*, 123, 85, 1943. (16.) Hansen-Pruss, O. C., and Goodman, E. G.: *Ann. Allergy*, 2, 85, 1944. (17.) Harkavy, J.: *J. Allergy*, 14, 507, 1943. (18.) Harkavy, J., and Romanoff, A.: *Am. Heart J.*, 23, 692, 1942. (19.) Hitzig, W. M., King, F. H., and Fishberg, A. M.: *Arch. Int. Med.*, 55, 112, 1935. (20.) Hoff, A., and Hicks, H. M.: *Am. Rev. Tuberc.*, 45, 194, 1942. (21.) Jackson, C.: *Am. J. Med. Sci.*, 156, 625, 1918. (22.) Karan, A. A.: *Ann. Int. Med.*, 17, 106, 1942. (23.) Kern, R. A.: *Internat. Clin.*, 3, 183, 1936. (24.) Kline, B. S., Cohen, M. B., and Rudolph, Y. A.: *J. Allergy*, 3, 531, 1932. (25.) Lamson, R. W., Butt, E. M., and Stickler, M.: *J. Allergy*, 14, 396, 1942. (26.) Lederer, R.: *Ztschr. f. Kinderh.*, 7, 1, 1913. (27.) Levine, S. A.: *Clinical Heart Disease*, 2nd ed., Philadelphia, Saunders, 1940. (28.) Lichtman, A. L., Stickney, J. M., and Kernohan, J. W.: *Proc. Staff Meet. Mayo Clinic*, 18, 500, 1943. (29.) Löffler, W.: *Schweiz. med. Wchnschr.*, 66, 1069, 1936. (30.) Maytum, C. K.: (a) *Med. Clin. North America*, 14, 729, 1930; (b) *J. Allergy*, 10, 50, 1938. (31.) Mendeloff, A. I.: *Ann. Int. Med.*, 22, 386, 1945. (32.) Miller, H., Piness, G., Feingold, B. F., and Friedman, T. B.: *J. Pediat.*, 7, 768, 1935. (33.) Mirvish, I.: *South African Med. J.*, 16, 431, 1942. (34.) Moll, H. H.: *Quart. J. Med.*, 9, 229, 1940. (35.) Paul, W. D.: *J. Iowa Med. Soc.*, 25, 643, 1935. (36.) Peshkin, M. M., and Fineman, A. H.: *Am. J. Dis. Child.*, 42, 590, 1931. (37.) Prickman, L. E., and Moersch, H. J.: *Ann. Int. Med.*, 14, 387, 1940. (38.) Rackemann, F. M.: (a) *Arch. Int. Med.*, 69, 128, 1942; (b) *J. Allergy*, 13, 622, 1942; (c) *New England J. Med.*, 230, 284, 1944. (39.) Rackemann, F. M., and Mallory, T. B.: *Trans. Am. Clin. and Climat. Assn.*, 57, 60, 1941. (40.) Rich, A. R.: *Bull. Johns Hopkins Hosp.*, 71, 123, 1942. (41.) Rich, A. R., and Gregory, J. E.: *Bull. Johns Hopkins Hosp.*, 72, 65, 1942. (42.) Santos, C.: *Rev. méd. latino am.*, 25, 508, 1940. (43.) Schiller, I. W., Colmes, A., and Davis, D.: *New England J. Med.*, 228, 113, 1943. (44.) Selye, H., and Pentz, E. I.: *Canad. Med. Assn. J.*, 49, 264, 1943. (45.) Smith, J. H.: *South. Med. J.*, 36, 269, 1943. (46.) Soysa, E., and Jayawardena, M. D. S.: *Brit. Med. J.*, 1, 1, 1945. (47.) Sprague, C. H.: *Connecticut State Med. J.*, 7, 399, 1943. (48.) Thieme, E. T., and Sheldon, J. M.: *J. Allergy*, 9, 246, 1938. (49.) Tocker, A. M., and Davidson, A. G.: *J. Allergy*, 15, 108, 1944. (50.) Urbach, E., and Loew, A.: *Am. Rev. Tuberc.*, 42, 174, 1940. (51.) von Meyenburg, H.: *Arch. f. path. Anat.*, 309, 258, 1942. (52.) Waldbott, G. L.: *Ann. Allergy*, 3, 12, 1945.

## NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF  
FRANKLIN G. EBAUGH

UNIVERSITY OF COLORADO, SCHOOL OF MEDICINE, DENVER, COLO.

AND

GEORGE S. JOHNSON

PROFESSOR OF PSYCHIATRY, STANFORD UNIVERSITY, SAN FRANCISCO, CALIF.

## THE AMYTAL INTERVIEW

BY BRIG. GEN. W. LEE HART, U.S.A.

COL. FRANKLIN G. EBAUGH, M.C., A.U.S.

AND

CAPT. DAVID W. MORGAN, M.C., A.U.S.

THE effectiveness of narcosis in revealing buried memories and conflicts has been recognized for hundreds of years, in fact as long ago as man has written about the effects of alcohol upon man. Much of the so-called newness of our narcosis treatments is a newness of terminology and a revival of older enthusiasms. Anesthetists long have remarked about how patients will reveal personal material and unrecognized facets of the personality during the induction phases of an anesthetic. The beneficial effects of emotional catharsis under the influence of an alcohol narcosis have been observed long before the treatment value of emotional episodes under newer narcotic methods was formalized into a new array of terms and esoteric discussions.

The newer methods of narcosis have been variously termed "narco-analysis," "narcosynthesis," "narcophypnoanalysis," "amytal interviews," and so forth. Horsley invented the term "narcoanalysis" in 1936,<sup>1,2</sup> and the term "narcosynthesis" was described by Grinker and Spiegel.<sup>3</sup> Bechterew had suggested that hypnosis, narcosis and sleep were closely allied.<sup>4</sup> As he pointed out, it is not readily easy to distinguish the differences between narcosis and hypnotic sleep. In fact, it is our opinion that the better results are obtained when the reactions of the narcotized patient are identical with similar reactions under hypnosis without the use of drugs. We do not agree with Grinker and Spiegel in differentiating the narcotic effects as distinct from hypnosis.<sup>3</sup>

Effective reliving and recovery of past experiences with amytal is similar to the use of hypnotic techniques without the benefit of drugs. In fact, barbiturates facilitate hypnosis for many subjects. Hypermnias, catalepsy, anesthetics, and post-treatment amnesias may be demonstrated while the patients are under the influence of amytal narcosis. In other words, the amytal interview is largely another hypnotic therapy.

Practically all of the modern barbiturates have been tried in various clinics. Chloroform, Cannabis Indica, paraldehyde, scopolamine and chloral often have been used for similar purposes.<sup>5,6,7,8</sup> We prefer to utilize the specific term, the amytal interview, because of greater acquaintance with the actions of the drug. Intravenous sodium amytal is preferred to pentothal because it is thought that one may prolong the milder levels of diminished awareness, when the usual techniques of hypnosis and suggestion may be reiterated over longer periods. There is no difficulty with "hang-over" effects from sodium amytal, if sufficient caffeine

sodium benzoate is used at the end of the treatment. Furthermore, it has been noted that one may suggest a selective recall of actions and discussions under amytal narcosis, like with hypnosis, more readily than with pentothal narcosis, largely because the lighter levels of narcosis are better controlled.

Hypnosis was used effectively in World War I, but for many reasons, technical, social and personal, few medical officers had acquired sufficient acquaintance with hypnotic techniques to use them effectively in World War II. The phenomena described by Grinker, Spiegel and others under the fancier terms of today were described by workers of the last war as manifestations of hypnotic therapy.

Brown,<sup>9</sup> Hadfield,<sup>10</sup> Taylor,<sup>11</sup> and Ross<sup>12</sup> were some of the enthusiastic exponents of the abreaction under hypnosis, which has acquired many semantic variations throughout the last 2 decades to become something "new."

The physiologic actions of the barbiturates on the cerebral cortex are well outlined by Brazier and Finesinger.<sup>13</sup>

"The work of Quastel and associates (Quastel, J. H., and Wheatley, A. H. N.: Narcosis and Oxidation of Brain, *Proc. Roy. Soc.*, London, 112, 60, 1932; Davis, D. R., and Quastel, J. H.: Dehydrogenations by Brain Tissue: Effects of Narcotics, *Biochem. J.*, 26, 1672, 1932; Quastel, J. H.: Respiration in the Central Nervous System, *Physiol. Rev.*, 19, 135, 1939) has shown that narcotics even in low concentrations inhibit specifically the oxidation *in vitro* by brain cells of d-glucose, lactic acid and pyruvic acid. This inhibitory action takes place, not by preventing the access of oxygen to brain cells nor by interfering with the activation of oxygen by brain catalysts, but by impairing the hydrogen-liberating mechanisms (dehydrogenase activity) which normally result in activation of lactic or pyruvic acid.

"Narcotics inhibit this dehydrogenase activity, presumably by forming surface films or adsorption compounds which prevent the access of hydrogen donors to their activating enzymes. (Sen, K. C.: The Effect of Narcotics on Some Dehydrogenases, *Biochem. J.*, 25, 849, 1931.) Thus, the effect of the narcotic is to diminish the ability of the brain cells to oxidize lactic or pyruvic acid or d-glucose. The access of oxygen to the cell is quite unimpaired, but the diminished oxidizing ability of the cells results in a lowering of the amount of energy available for these cells to accomplish their functional activities. This depression of the normal functional activity of the cells in question results in, or is, 'narcosis.'

"The chain of oxidative processes in brain cells may be represented in outline by the following simplification: At the beginning of the chain the principal substrate is d-glucose, which, through a long chain of intermediary changes, is finally oxidized to carbon dioxide and water, with liberation of large amounts of energy. One of the chief intermediary stages in the first part of the breakdown of d-glucose is the oxidation of lactic acid to pyruvic acid. Meyerhof (Ueber die Atmung der Froschmuskulatur, *Arch. f. d. ges. Physiol.*, 175, 20, 1919) showed the dependence of this stage on the presence of a coenzyme which acts as a specific carrier linking lactic dehydrogenase with lactic acid in such a way that the dehydrogenase can remove hydrogen from the lactic acid, with the production of pyruvic acid. The dehydrogenase which activates lactic acid as a hydrogen donor is highly specific. (The dehydrogenase which activates lactic acid has been isolated, and its chemical constitution is known.—Schlenk, F.: Whither Enzyme Chemistry, *Texas Rep. Biol. and Med.*, 2, 183, 1944) and is present in greater quantities in brain than in muscle (Green, D. E., and Brotteaux, D.: Lactic Dehydrogenase of Animal Tissues, *Biochem. J.*, 30, 1489, 1936).

"It is this stage of dehydrogenase activity which is inhibited by narcotics of the barbiturate type. To repeat, these narcotics do not interfere with the catalytic activation of oxygen, or with the access of oxygen to the brain cells, but inhibit the activity of the dehydrogenase stages of pyruvic and lactic acid metabolism.

"The mechanism of this dehydrogenase activity may well be, as Quastel and

Wooldridge (Some Properties of Dehydrogenating Enzymes of Bacteria, *Biochem. J.*, **22**, 689, 1928) suggested, a polarization of the molecule of the substrate by an electric field at the cell surface to which the molecule is attached. If the polarization is sufficient, the molecule will receive its critical energy of activation and will then be able to function as a hydrogen donor.

"This chain of events in the cell respiration of brain tissue has been worked out from data gained from *in vitro* experiments with minced fresh brain and with brain slices, variations of the Barcroft and Warburg techniques (Dixon, M.: *Manometric Methods*, London, Cambridge University Press, 1934) being used for the most part. To extend these studies to the respiration of brain cells *in vivo* necessitates some other technic. Electroencephalography may well furnish pertinent data in this field.

"The work of Hoagland (*a.* Hoagland, H.: *Chemical Pacemakers and Physiological Rhythms*, in Alexander, J.: *Colloid Chemistry*, New York, Reinhold Publ. Corp., vol. 5, 1944; *b.* *Pacemakers of Human Brain Waves in Normals and in General Paretics*, *Am. J. Physiol.*, **116**, 604, 1936; *c.* Hadidian, Z., and Hoagland, H.: *Chemical Pacemakers: I. Catalytic Brain Iron; II. Activation Energies of Chemical Pacemakers*, *J. Gen. Physiol.*, **23**, 81, 1939) demonstrated clearly the influence of changes in brain cell respiration on the frequency rates of cortical potentials. It is probably that cortical cells build up potential gradients in the process of their respiratory metabolism, and, as Hadidian and Hoagland (*c.* above) stated:

"These may be of the nature of diffusion potentials across cell membranes which possess definite electrical impedance and which discharge when the potentials reach a critical value. In such a system the discharge frequency depends on the speed with which the metabolic factor can load the capacities of the cell walls to their critical discharge potentials. The absolute frequency would thus depend on the rate of cellular respiration and on the electrical impedance of the cell walls.  
...."

The technique of the sodium amytal interview is simple. Dilute 15 gr. (1 gm.) of sodium amytal in 30 or 40 cc. of distilled water. Place this solution in a large enough syringe and use a small gauge intravenous needle to provide further protection against too rapid administration of the drug. The solution should not stand for over 30 minutes before use, and it should be clear. In fact, it is preferable to check the preparation of the solution to be sure of proper mixing and proper dosage.

Always have  $7\frac{1}{2}$  gr. of caffeine sodium benzoate ready in a hypodermic syringe in case of untoward reactions or too deep a narcosis. At the completion of the interview it is well to administer  $7\frac{1}{2}$  gr. of caffeine sodium benzoate subcutaneously to assure one against prolonged deep narcosis and to facilitate the return of awareness. If sleep ensues before the interview is well under way, it is wise to give the caffeine intravenously or subcutaneously to quicken the awakening so that the interview may be carried on without undue delay. Remember, it is imperative to have a stimulant on hand for instantaneous use. Do not compromise this principle.

It is well to have a quiet room, dimly lit and empty, except for the bed and a chair or two. This affords better protection for the patient, if you stir up a violent combat reaction. The patient should not have any breakable object on his person, and it is preferable to have him dressed in pajamas. It is assumed that some time has been spent beforehand in developing confidence and understanding of the purposes of the treatment. The better the relationship between the patient and the doctor the more frequently and more readily one will obtain effective results. The skillful use of suggestion makes a great difference. One should be well acquainted with the routine techniques of hypnosis, and one should repeat with confidence a number of suggestions directed toward relaxation and sleep.

These suggestions should be made so that they will fit in with the background of the patient's understanding and personality. Occasionally this will not apply to very hostile and resistive patients. For this type of patient the amytal session may be the quicker and more effective way to erase the barriers to deeper understanding and control of unbridled aggression.

The sodium amytal should be administered very slowly, more slowly than at the rate of 1 gr. per minute. During the administration of the drug it is well to begin with neutral topics regarding the past life of the patient and gradually to work into the military history. When the patient begins to speak more freely or in a mush-mouthed manner, then it is well to try to stimulate a return to combat by using alert signals ("condition red, blasts on a siren, etc.") and by strong and repeated suggestions that the patient is "on the line" in the area of his most severe combat experience ("hill 69, bloody knoll," etc.). Set up a combat situation, and try to get the patient to go through the commands and action of the day, taking the rôle of the persons to whom he calls for help or advice. This means that you must have an acquaintance with military terminology, slang and the local ground rules in the combat area from which the patient has come. This is best obtained in previous interviews with the patient wherein you will learn of the alert signals, the areas of the toughest action, the names of his subordinates and his superiors, the location of the command post and the patient's rôle in the action.

If this does not strike a response, then it is well to systematically explore the immediate situation and complaints, trying to trace their origins and relationship to the past. In this connection it is invaluable to stimulate a recall of dreams and recent phantasies. The recent dreams are very productive of clearer insights into forgotten traumatic events, conflicts, and so forth. It is relatively simple to allow the patient to make associations with the content of the dream and to aid him in pointing toward the meaning of such dreams.

The therapist's skill in dramatizing the combat situations may determine the richness of the interview. Battle records, simulated alert signals and so forth will help to strike action from the patient. Even when the events of combat have not been emotionally upsetting, it is possible to have the patient relive the experiences of the line; we have observed the work of some outstanding combat men as they go through an action and direct the men under them with precision and coolness.

Except with combat cases, there is little need to deviate from the routine skills and techniques of interviewing. However, it is well to *save the more delicate probing for the later stages of the interview when you are assured of a deep "sleep."* For example, when you are trying to determine the validity of hallucinatory material it is well to wait until a deep level of "sleep" is achieved before direct questions are given. However, under narcosis it is easier to go directly to the tender areas or the forgotten episodes by pointed questioning.

The depth of narcosis is difficult to determine, and one learns when to stop the administration of the drug by experience. Soon one learns to appreciate a sudden relaxation, a lid-flickering, slower and more regular breathing, a more rapid flow of ideas and a quicker response to questioning. Skill in knowing when to stop is important, for it is easy to get too deep a level of narcosis. It is well to administer the drug very slowly in the beginning of one's experience and to continue with the interview from the

beginning to the end of the injection. Be ever alert for changes in muscle tension, the cessation of a tremor, the absence of blocking, and so forth. These signs are valuable indicators of when to stop giving the drug. If in doubt, it is easy to try some direct suggestions and to note the effect. If narcosis is not deep enough, you will readily observe it.

It has been our experience that much more of the drug is needed for a very hostile or resentful patient and that it is not unusual for us to give from 8 to 10 gr. of sodium amytal to get proper relaxation and narcosis with resistive subjects. In fact, it has been our experience that the amount of drug administered is a good index of the amount of resistance toward narcosis. It is surprising how bitter and resentful subjects may resist the effects of amytal. This is particularly true when you are using the method in legal work with criminals. Then, too, we did not begin to get effective results with conversion symptoms until we began to use larger doses, that is, above  $7\frac{1}{2}$  gr., and now we are convinced that resistance is a good antidote and that you should slowly push the medication until the desired level of narcosis is reached, regardless of the amount needed. To date, we have not exceeded 15 gr. and have only rarely had to use that much. Only 1 case of respiratory arrest has been observed in the treatment of over 500 cases, and this was after the giving of less than 4 gr. of sodium amytal. This was a patient unusually susceptible to the narcotic effect, and we had given the medication too rapidly. However, the administration of 15 gr. of caffeine intravenously was followed by a prompt return of respiration.

Tension and resistance seems to raise the threshold to narcotic effects like pain raises the threshold to morphine effect. Furthermore, it is precisely with cases that do exhibit marked resistance and tension that amytal proves often more effective than other less direct approaches to treatment.

We have made no tabulations of results with the use of amytal narcosis in the treatment of our cases. Yet we have, over the last year, obtained certain definite impressions regarding the value of this therapeutic approach. The technique is valuable in relatively unskilled hands, and training in the usage of the amytal interviews is a relatively simple task. Furthermore, amytal is more widely effective when it is given in sufficient quantities to produce appreciable clouding of consciousness and thickness of speech.

As a beginning for the discussion of the values of the amytal interview it may be well to list some of the effective applications:

1. Recovery of forgotten or painful experiences and conflicts.
2. Reliving of emotionally traumatic experience.
3. Aid in differential diagnosis.
4. Treatment of hostile and resentful patients.
5. Uncovering faking and conscious distortions.
6. Uncovering hallucinatory material.
7. Treatment of conversion symptoms (limps, backaches and so forth).
8. Facilitate hypnotic treatments.
9. Control of excitements, panics and rage reactions.
10. Clarification of amnesic episodes.
11. Treatment of mute or catatonic patients.
12. Correction and clarification of psychogenic components of structural disorders:
  - (a) Orthopedic problems.
  - (b) Post-traumatic head syndromes.



## 13. Aid in legal psychiatric work:

- (a) Questioning of suspected thieves, and so forth.
- (b) Questioning regarding facts in self-mutilation.
- (c) Clarification of so-called "AWOL or drunken amnesias."

## 14. Aid in re-testing when conscious distortions or inadequate coöperation is suspected:

- (a) Intelligence testing.
- (b) Rorschach testing.

The amytal interview is very effective as therapy for combat cases of relatively recent origin, for recovery of forgotten or painful battle experience and for the reliving of the emotionally traumatic situations. It helps very much in establishing a firm basis for effective therapy and interpretation. We think that the reliving of the emotional experiences is beneficial, and we have observed that battle dreams, sleeplessness, irritability, associability and negativistic reactions subside promptly after an effective treatment. The more lasting effects can be established by interpretation of this material during the next 2 or 3 days following the treatment. The amytal interviews should be repeated until one attains a much quieter reaction or observes no marked emotionally tinged battle experiences like the ones observed at the first or second treatment. More often it has been true that only 2 or 3 treatments are necessary as long as they are followed through by careful interpretation and elaboration of the material when the patient is alert.

The differential diagnosis of schizophrenic reactions is facilitated by amytal sessions. On a number of occasions we have been able to demonstrate hallucinatory material that had been present but not revealed during the earlier days of hospitalization. Then, too, we have observed questionable psychotic reactions where the facts have been much clearer under amytal. For example, one prisoner who attempted to imitate an acute psychotic episode that had been observed by him during a previous prison stay admitted the falsification under amytal. Furthermore, where one has some local structural damage with a functional overlay, it is very helpful to give amytal to evaluate the amount of structural and functional disability. From this evaluation one may proceed to make a more direct interpretation of the functional elements.

Also, resentful and negativistic patients respond to amytal sessions given within the first day or two of admission and thereby reduce the time necessary for developing a clearer understanding of the origins of the hostility and resentfulness. These patients need a much larger dose of sodium amytal. Occasional striking results have been obtained from prompt use of amytal interviews for this type of reaction. Likewise, the same approach has given great help with mute and catatonic patients and has facilitated the ward management of that type of case.

A correlated problem deals with patients who claim that they cannot speak English, particularly Mexican patients. Under amytal one may be able to demonstrate a much better grasp of English. Likewise, where we have clinically estimated a greater intelligence than was demonstrated through intelligence testing, we have at times been able to get a more reliable estimation under amytal. This applies to other types of tests like the Rorschach and the Shipley-Hartford Retreat Scale. It is simple to repeat a test during an amytal interview when the examiner is unsatisfied with the productivity of the patient during the wakeful state.

We had 4 or 5 cases of malingering where we have been able to demonstrate this conscious faking during the amytal sessions. It is our impres-

sion that sodium amytal interviews are particularly valuable where faking or conscious distortions are suspected.

The use of amytal sessions in the treatment of conversion symptoms has been described before. We find it particularly helpful in demonstrating functional limps and backaches, but our results have been erratic. With the Negro patients we have had very poor results. With a few of the intelligent white patients we have had rather prompt recoveries and have been able to interpret the meaning of the conversions to the patient within a short time.

It is obvious that sodium amytal can be used in the control of excitements, panics and rage reactions, like any sedative. However, it would be wiser to give the amytal intramuscularly instead of trying to struggle with the patient to give an intravenous dosage. The use of sodium amytal in the recovery of amnesic episodes has been previously described, and its use is valuable for cases that show extensive amnesias.

Skill in the use of amytal is a necessary art in the adequate practice of military psychiatry, and one may attain this skill by using the method sufficiently to become acquainted with effects and results upon patients well known to the doctor. Skill in the use of amytal or a similar agent will provide the therapist with another valuable and rapid type of treatment and diagnostic agent.

#### REFERENCES

- (1.) Horsley, J. S.: Narco-analysis, *J. Ment. Sci.*, **82**, 416, 1936. (2.) Blyth, W.: Pentothal Sodium Narcoanalysis, *J. Ment. Sci.*, **88**, 504, 1942. (3.) (a) Grinker, R. R.: Conference on Narcosis, Hypnosis and War Neuroses, sponsored by the Josiah Macy, Jr. Foundation, New York., 1944 (private distribution). (b) Grinker, R. R., and Spiegel, J. P.: War Neuroses in North Africa: The Tunisian Campaign (January to May, 1943), Josiah Macy Jr. Foundation, New York, 1943. (4.) Bechterew, W. V.: What is Hypnosis., *J. Abn. Psych.*, p. 18, April, 1906. (5.) Bramwell, M.: Hypnotism: Its History, Practice and Theory (revised), Philadelphia, Lippincott, 1928. (6.) Schilder, P., and Kauders, C.: Hypnosis, Nervous and Mental Disease Monograph, **46**, 118, 1928. (7.) Breotiaux, P.: (a) Hypnotisme et Scopoloralose, Paris, 64 pp., 1936; (b) L'hypnotisme Moderne, Paris, 83 pp., 1938. (8.) Stungo, E.: Evipan Hypnosis in Psychiatric Outpatients, *Lancet*, vol. 1, 1941. (9.) Brown, W.: (a) Hypnosis in Hysteria, Letter to the editor of *The Lancet*, **15**, 505, 1918; (b) Hypnosis, Suggestibility and Progressive Relaxation, *Brit. J. Psych.*, **28**, 396, 1938; (c) Psychology and Psychotherapy, London, Edward Arnold, 252 pp., 1934; (d) The Treatment of Cases of Shell-shock in an Advanced Neurological Centre, *Lancet*, **2**, 197, 1918; (h) Brown, W., Myers, C. S., and McDougall, W.: Symposium on the Revival of Emotional Memories and Its Therapeutic Value, *Cf. No.* 189. (10.) Hadfield, J. A.: Chapter on Treatment by Suggestion and Hypnoanalysis, in the Neuroses in War, edited by Emanuel Miller, New York, Macmillan, 1940. (11.) Taylor, W. S.: (a) Behavior Under Hypnoanalysis and the Mechanism of the Neurosis, *J. Abn. Psych.*, **18**, 107, 1923; (b) A Hypnoanalytic Study of Two Cases of War Neurosis, *J. Abn. Psych.*, **16**, 344, 1921-22. (12.) Ross, T. A.: (a) The Common Neuroses, Baltimore, William Wood, 233 pp., 1937; (b) The Prevention of Relapse of Hysterical Manifestations, *Lancet*, **2**, 516, 1918; (c) Prognosis in the Neuroses, Cambridge, University Press, 194 pp., 1936. (13.) Brazier, M., and Finesinger, J. E.: Action of Barbiturates on the Cerebral Cortex—Electroencephalographic Studies, *Arch. Neurol. and Psychiat.*, vol. **53**, No. 1, 1945.

#### PHYSIOLOGY

##### PROCEEDINGS OF

##### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 15, 1945

The Necessity of Fluorine in the Diet of the Rat.\* J. F. McCLENDON and Wm. C. FOSTER (Dept. of Physiology, Hahnemann Med. Coll.). Since

\* Aided by a grant from the Aluminum Company of America.

all foodstuffs we analyzed contained fluorine, we used fluorine-free corn, sunflowers, soy beans and yeast grown by hydroponics. To avoid the fluorine in city air, a greenhouse was built on Trooper Road. Traces of fluorine in rain water from a glass roof were removed by acid exchange resin, amberlite IR4. Fluorine was removed from reagent nutrient salts by making a stock solution about pH 12 and before more than 10% of the calcium phosphate precipitated filtering by suction into enough fluorine-free sulfuric acid to bring the pH to 4.5 and diluting to prevent the precipitation of gypsum. The solutions were analyzed often and air pumped to the roots. Two rats, which had just been weaned, on this diet were dying in 48 days but 1 was revived with fluorine-containing milk and died in 70 days. The addition of 1% calcium citrate containing 0.4 ppm. fluorine improved the health of 5 other rats on this diet. One was killed at 56 days, 1 at 70 days and 3 are living at 74 days. Since rats in the wild state do not have mineral supplements and all calcium salts seem to be made from CaO containing 4 to 6 ppm. fluorine which accompanies the calcium through purification processes, we think the diet without additional calcium justified. Soy beans contain 0.25% calcium and sunflower seeds 0.2%. Fluorine is passed from mother to offspring and the less fluorine in the mother's diet, the fewer young are born and the less is the milk supply of the mother. All these rats had extensive decay of the molar teeth; in some cases all of the crowns were lost.

---

**Somatic Factors in Electroencephalography.** T. CUNLIFFE BARNES (Dept. of Physiology, Hahnemann Med. Coll. and Hosp. of Phila.). In 46 persons, 28 gave abnormal delta EEGs in overventilation; 18 had good vital capacities and 10 poor. In the 18 that gave normal EEGs in overventilation, 13 had poor and only 5 had good vital capacities. A good vital capacity produces sufficient hypocapnia to slow the EEG. Of 22 army medical students, 11 had 90 to 130 mg. per 100 cc. blood sugar (non-fasting), and most showed abnormal overventilation EEGs, while 11 with levels of 130 to 160 had few abnormal waves in overventilation EEGs. Blood sugar enables the brain to withstand the vasoconstriction of hypocapnia. In 23 persons with abnormal overventilation EEGs, the pulse rose 26 beats per min. (average), while in 10 with normal overventilation EEGs, the pulse rise was only 15 beats. In 11 cases with abnormal overventilation EEGs, the skin temperature (thumb) fell 1.7° C. (average), and in 6 cases with normal overventilation EEGs the skin temperature rose 0.2° C. The rising pulse and cooling skin indicates sympathetic vasoconstriction producing slow ischemic EEGs in deep breathing, which may be overcome by a strong parasympathetic component. Of 15 regular breathers, 13 had low alpha waves in occipital lobes (visual imagery) in contrast to 12 irregular breathers (laryngeal component of auditory imagery) who had inactive visual centers (alpha over 70%).

Fourteen schizophrenics had an average alpha index of 23% (5 had no alpha), 10 manics had alpha index of 44% (1 had no alpha). Of 25 schizophrenics, 16 had regular pneumogram and 10 of 21 manics had regular breathing. The depth of the breathing recorded by a Marey tambour gave the most striking difference—3 mm. for schizophrenics and 9 mm. for manics. A regular, very shallow pneumographic record seems characteristic of dementia præcox except during violent hallucinations. Seven of 9 schizophrenics with auditory hallucinations had irregular pneumograms (as predicted from normals).

Brain waves are taken to be phase-boundary potentials produced by acetylcholine. Benzyl alcohol (inactive with acetylcholine) containing 37% fresh human cortex generates 12 mv. negative with 0.05% acetylcholine (in Dr. Beutner's oil-cell).

---

**Experience With Mild Exercise as a Test for the Convalescent State.\*** ISAAC STARR, R. MAYOCK and M. G. BATTLES (Hartzell Research Dept. of Therapeutics and Harrison Dept. of Surgical Research, Univ. of Penna.). By means of a standard exercise test, lifting a 10 pound iron bar from the chest to arms length above it, we have sought to demonstrate physiologic abnormalities during convalescence from surgical procedures.

Oxygen consumption and volume and rate of respiration have been determined before, during, and after standard exercise. Cardiac output (ballistocardiogram) and pulse rate were estimated before, just after, and 5 minutes after the same standard exercise.

Measurement of the *amount* of the changes induced by the exercise revealed no significant differences which could be attributed to convalescence. However, when attention was given to the duration of the changes induced by the exercise, the averages showed significant differences, the increased oxygen consumption, respiration, and pulse rate declining to the resting level more slowly during convalescence than before operation.

The resting respiration and oxygen consumption were not significantly changed during convalescence.

The variability in the physiologic response to exercise was so large that a test of the type used gives no promise of providing a satisfactory measure of the duration of convalescence in individual cases. However, the slow return to normal of pulse rate, respiration, and oxygen consumption after exercise is over may have some value as an indication of persisting abnormality in certain individuals and will provide significant differences when data obtained from a series of 10 or more cases are averaged.

---

**Dietary Requirements for Nitrogen Equilibrium in the Period Immediately Following Certain Major Surgical Operations.\*** C. RIEGEL, J. E. RHOADS, C. E. KOOP, R. P. GRIGGER, L. BULLITT and D. BARRUS (Harrison Dept. of Surgical Research, Univ. of Penna.). Surgical patients kept on the usual hospital régime following gastric and cranial operations were found to be in negative nitrogen balance during the first 5 postoperative days. By placing such patients on a diet by mouth or Abbott-Rawson tube containing approximately 0.25 gm. nitrogen and 25 calories per kilogram daily, or over, a majority could be brought into positive nitrogen balance. The types of food used were: (1) regular mixed house diet, (2) Amigen (Mead Johnson & Co.), (3) Amigen plus house diet, (4) gastrostomy mixture (milk, skim milk powder, egg, cottage cheese, soy bean flour) and (5) lactalbumin hydrolysate. Both hydrolyzed protein and whole protein at this level were equally effective.

Patients fed intravenously at this same level with gelatin alone or Amigen alone were in negative nitrogen balance, suggesting that intravenous feeding is perhaps not as effective as tube feeding.

Plasma protein concentration often increased when patients were given

\* Work done under contract with the Office of Scientific Research and Development.

special feeding, even though they were not given over 0.25 gm. nitrogen and 25 calories per kilogram or were not in nitrogen equilibrium.

Weight loss in patients on diets of 0.25 gm. nitrogen and 25 calories per kilogram daily was less than in those patients kept on the usual hospital régime.

---

**The Effect of Ultra-violet Irradiation on the Toxicity and Chemotherapeutic Action of Stilbamidine.** L. D. SEAGER, G. R. WELLS, and GINA CASTELNUOVO (Depts. of Pharmacology and Anatomy, Woman's Med. Coll. of Penna.). Solutions of the various salts of stilbamidine are fluorescent. On irradiation by ultra-violet light this property is altered and, as shown by Fulton and Yorke, the toxicity for mice is increased 6 to 8 times. According to Henry, some of the stilbamidine is changed from the trans to the cis form and some is changed to 1, 2, 4, 5 tetra (4 amidino phenyl) cyclobutane. In experiments on dogs we have found that the irradiated compound produces a greater fall in blood pressure than the non-irradiated drug. In 5 dogs the dosage of the irradiated solution was altered until equivalent changes in pressure were produced to those of a standard dose of the non-irradiated drug. The depressor effect was potentiated 3 to 4 times. With equal falls in pressure however, the irradiated solution gave a more prolonged depressor effect. Mice inoculated with *T. equiperdum*, 1,000,000 per kg., were treated with varying doses of the irradiated and the non-irradiated compounds. The agents were given orally 3 times daily for 4 days. The ED 50 for bringing about the cure of the infection was between 1 and 1.2 mg. per kg. for the normal drug, and between 3 and 4 mg. per kg. for the irradiated solution. Boiling solutions of the drug for 2 hours did not alter its toxic or therapeutic properties. It is apparent that irradiation increases the toxicity of stilbamidine 3 and 4 times, but reduces its chemotherapeutic effect to a similar extent.

# BOOK REVIEWS AND NOTICES

---

AN INTRODUCTION TO SOMATIC METHODS OF TREATMENT IN PSYCHIATRY. By WILLIAM SARGANT, M.A., M.B. (CANTAB.), M.R.C.P., D.P.M., Medical Officer, Maudsley Hosp., and ELIOT SLATER, M.A., M.D. (CANTAB.), M.R.C.P., D.P.M., Medical Officer, Maudsley Hosp. Pp. 171. Balt.: Williams & Wilkins, 1944. Price, \$2.50.

In this book is found a battery of physiochemical therapies for the psychoses—insulin and electric shocks, continuous sedations, vitamins and endocrines and others. On one hand these procedures link psychiatry with general medicine; on the other they fight the great discourager in psychiatry—chronicity.

The chapter on insulin shock is detailed and trustworthy. The remarks on depth of stupor and treatment of prolonged stupor should be followed by a reading of 1944 articles by Himerich and Rivers and Rome, which go more deeply into the subject. The various treatments of the epilepsies make an interesting section because of the new suggestions and controls opened up by the electro-encephalograph. The authors put a discussion of psychotherapy as a help to somatic means in a final short chapter.

This is a sound, stimulating book for the beginner in psychiatry. There is no bibliography. E. B.

---

MANUAL OF TROPICAL MEDICINE. Prepared under the Auspices of the Division of Medical Sciences of the National Research Council. By COL. THOMAS T. MACKIE, M.C., A.U.S. (and 8 others). Pp. 727; 287 ills., 6 in color. Phila.: Saunders, 1945.

THIS is an excellent example of printing and binding; but, as a presentation of the essentials of Tropical Medicine, it leaves something to be desired. Not that it does not contain essentials and more, as indicated by the following chapter headings: The Viruses, Rickettsial Diseases, Spirochetal Diseases, Bacterial Diseases, Protozoal Diseases, Helminthic Diseases, Nutritional Diseases, Miscellaneous Conditions, Medically Important Arthropods and Laboratory Diagnostic Methods. The "Miscellaneous Conditions" are Bartonellosis, Tropical Ulcer, Desert Sore, Cutaneous Diphtheria, Granuloma Inguinale; Scabies, Effects of Heart, and Certain Medically Important Animals. The general plan of the book is said to be more or less the same as the course in Tropical and Military Medicine as presented by the authors and their colleagues at the Army Medical School. All of this is excellent and so are the many photographs and charts which illustrate the book; but the text is not well written. In fact it makes unnecessarily difficult reading. This is not only my opinion but also that expressed by undergraduate medical students to whom the book had been assigned. These might not be regarded as major faults in the discussion, but lack of coherence in one place or wordiness in another can only discourage an overworked student. The text hardly justifies the title "A Manual of Tropical Medicine."

H. R.

---

ON MODERN SYPHILOTHERAPY WITH PARTICULAR REFERENCE TO SALVARSAN. By ALBERT NEISSER. Translated by ISABELLE VON SAZENHOFEN WARTEBERG. Pp. 42. Balt.: Johns Hopkins Press, 1945. Price, \$1.00.

THIS reprint from *The Bulletin of the History of Medicine* (16, 469, 1944) contains a biography of Albert Neisser and a bibliography of his works by Frances Tomlinson Gardner, together with a translation by Isabelle von Sazen-

hofen Wartenberg, of his article, "On Modern Syphilotherapy With Particular Reference to Salvarsan."

J. E. Moore has recently (*Am. J. Syph., Gonorr. and Ven. Dis.*, 29, 185, 1945) stated that "the chemotherapy of syphilis is divisible into three periods of very unequal length: the first lasting 410 years, from 1493 to 1903; the second 40 years, from 1903 to 1943; the last, in which the doors of knowledge have as yet opened only a tiny crack, for 16 months, from June 1943 to the present moment." Now that we are in the midst of the third—penicillin era—it is refreshing to read a first-hand presentation of principles by one of the pioneers of the second period which up to now has been called "modern" syphilology. The content of Neisser's dissertation is very timely, as experience with penicillin is emphasizing more and more that many of the facts he stressed, prolongation of treatment, combined treatment, and so forth, are applicable to effective penicillin therapy of syphilis.

The biographer has given a sympathetic and touching sketch of Neisser, and the bibliography indicates the range of his busy scientific life.

The book, considering wartime restrictions, is attractively presented. The Reviewer believes everyone interested in syphilology should read this volume.  
H. B.

**TROPICAL MEDICINE.** By SIR LEONARD ROGERS, K.C.S.I., C.I.E., LL.D., M.D., B.S., F.R.C.P., F.R.C.S., F.R.S., Major-General, I. M. S., Ret., Physician and Lecturer, Lond. School of Trop. Med.; Lecturer on Trop. Med., Lond. School of Med. for Women; Late Professor of Pathology, Medical Coll., Calcutta; and SIR JOHN W. D. MEGAW, K.C.I.E., B.A., M.B., Hon. D.Sc. (Queen's Univ., Belfast), Major-General, I. M. S., Ret., Late Lecturer, Lond. School of Trop. Med.; Director-General, Indian Med. Serv.; and Director and Professor of Trop. Med., Calcutta School of Trop. Med. and Hyg. 5th Ed. Pp. 518; 2 colored plates and 87 text-figures. Baltimore: Williams & Wilkins, 1944.

The 5th edition of this book in less than 15 years speaks for itself. It also reflects well the high places of the authors in the field of Tropical Medicine. Not only is this book a product of long personal experience both in teaching and research, but, equally important, it is well written. Of the illustrations (charts and maps), the charts which portray insect-borne disease are especially good. They combine the development of pathogens in the vectors with the story of the diseases in man, giving the time in days required for the vector to become infective, the fate of the organism in the vector, incubation period for man, mode of onset, temperature curve and other distinctive changes. Directions for treatment reflect the views and background of the authors and could have been presented more effectively by tabulation. In this respect it may be noted that quinacrine (atabrine) does not receive the place it deserves in the therapy of malaria. There are other examples of conservatism in the book, but these do not lessen its value. It can be recommended as a brief but adequate discussion of Tropical Medicine. H. R.

**OUTLINE OF THE AMINO ACIDS AND PROTEINS.** By MELVILLE SAHYUN, M.D., Ph.D., Vice-President and Director of Research, Frederick Stearns & Co. With 13 contributing authors. Pp. 251. New York: Reinhold Pub. Corp., 1944. Price, \$4.00.

INTEREST in problems dealing with proteins and amino acids has developed widely in many fields of biologic and medical sciences. Students will find this book of particular interest for its presentation of the elements of the chemistry and biochemistry of the amino acids and proteins in a simple, readable manner.

The subject is presented in 12 chapters by qualified contributing authors: Discovery of the Amino Acids (Melville Sahyun); Occurrence, Amino Acid Content and Properties (C. L. A. Schmidt); Protein Structure (H. B. Bull);

Hydrolysis of Proteins (Melville Sahyun); Synthesis and Isolation of Certain Amino Acids (H. E. Carter and I. R. Hooper); Methods of Analysis for Amino Acids and Proteins (D. M. Greenberg); Relation of Amino Acids and Their Derivatives to Immunity (Michael Heidelberger); Relation of Amino Acids to Biologically Important Products and the Role of Certain Amino Acids in Detoxication (A. J. Quick); Metabolism of Proteins and Amino Acids (W. M. Cahill); Intermediary Metabolism of Individual Amino Acids (W. M. Cahill); Nitrogen Equilibrium and the Biological Value of Protein (W. M. Cahill and A. H. Smith); Amino Acids and Proteins in Nutrition (Madelyn Womack and C. F. Kade).

Approximately half of the book is concerned with fundamental chemistry of the amino acids and proteins; the remainder is devoted to biochemistry and metabolism. There is considerable duplication in the information presented in the last 5 chapters, as can be predicted from the titles of the chapters. Adequate bibliographic references to current literature are appended to each chapter, and an appendix lists U. S. patents issued on amino acids and related organic compounds.

H. V.

THE ETIOLOGY, DIAGNOSIS, AND TREATMENT OF AMEBIASIS. By CHARLES FRANKLIN CRAIG, M.D., M.A. (HON.), F.A.C.S., F.A.C.P., Col., U.S.A., Retired, D.S.M.

AMEBIASIS and amebic dysentery are as widespread as fecal contamination of food and drink. This is an established fact of many years standing, but so often is it overlooked or forgotten that it might just as well be a new discovery. Explanation of this state of affairs is not difficult. First, textbooks published in the United States commonly draw on material from North China, the Philippines or Panama. Thus *Endamæba histolytica* comes to be associated with the tropics or with poorly sanitated regions of the Orient. With little more effort, authors might just as well illustrate their texts with cases that are buried in the records of every northern hospital of any size. Another and perhaps more important block to recognition of clinical cases of amebiasis is microscopic examination of feces. This is a difficult and unpleasant task. It cannot be trusted to the average laboratory technician, and, until it may be or until the "higher brass" may be persuaded to accept this responsibility, the great majority of cases of amebiasis will pass undiagnosed. Fortunately most of them tend to be relatively mild.

More than any other American author Colonel Craig has attempted to stimulate justifiable interest in amebiasis in this country. In numerous papers and addresses he has discussed epidemiology, diagnosis and treatment and in 1934 Charles C Thomas published his monograph "Amœbiasis and Amœbic Dysentery." This book under review is essentially a revision of this monograph. It is an up-to-date consideration of infection by *Endamæba histolytica* and, if it receive the attention which it and this infection warrant, fewer cases of amebiasis and amebic dysentery will go undiagnosed.

H. R.

PATHOLOGY OF LABOR, THE PUERPERIUM AND THE NEWBORN. By CHARLES O. McCORMICK, A.B., M.D., F.A.C.S., Clinical Professor of Obstetrics, Indiana Univ. School of Medicine; Consulting Obstetrician to William H. Coleman Hosp. for Women, Indianapolis City Hosp. and Sunny Side Sanitarium. Pp. 399; 191 figs. St. Louis: Mosby, 1944. Price, \$7.50.

THIS volume is based upon the author's lectures prepared for senior medical students. The material is presented in the form of a synopsis, arranged with numerous paragraph headings, and the majority of the facts are arranged numerically. Its condensed form makes it ideal as a means for preparing for examinations. The disadvantage of such a form of preparation lies in the fact that it tends to place a premium on memorizing.

D. M.



**DUODENAL AND JEJUNAL PEPTIC ULCER.** By **RUDOLF NISSEN**, M.D., Attending Surgeon, Jewish Hosp. of Brooklyn; Member, Medical Advisory Board, National Jewish Hosp. of Denver; Formerly Professor of Surgery and Head of Department of Surgery, Univ. of Istanbul; and Associate Professor of Surgery, Univ. of Berlin. Pp. 143; 123 figures. New York: Grune & Stratton, 1945. Price, \$4.75.

THIS book deals with the surgical technique of gastro-duodenal resections for duodenal ulcer. It is adapted for those engaged in gastric surgery.

The first part presents the various techniques of resection for duodenal ulcer along with an evaluation of the results to be expected. The author includes his own technique of resection and closure of the duodenal stump in penetrating ulcers of the posterior duodenal wall. The second part is devoted to the technique of resection of postoperative marginal ulcers and fistulas. A 2-stage operation is presented for poor risk patients.

The book is well illustrated, and the subject matter is clearly presented. It should be of value to all who are concerned with the technical aspects of surgery of ulcers and particularly with the more complicated problems for which secondary operations are required. R. P.

**THE NEW YORK HOSPITAL.** A History of the Psychiatric Service (1771-1936).

By **WILLIAM LOGIE RUSSELL**, Professor of Psychiatry, Emeritus, Cornell Univ. Medical Coll.; Consulting Psychiatrist, New York Hosp. Pp. 556. New York: Columbia Univ. Press, 1945. Price, \$7.50.

As is stated on the cover, "this work gives an account of the earliest, and for almost 50 years, the only provision for the hospital treatment of the mentally ill in the state of New York. The project was instituted in 1771, by a small group of physicians and other private citizens in connection with the establishment of a general service and teaching hospital in New York City . . . Physicians, nurses, hospital managers, and others officially concerned with the problems of mental illness will find encouragement and guidance in the experiences related. In addition, this intimate account of the development of a well-controlled and liberally supported service will be useful to teachers and students of psychiatry and mental hygiene and to those interested in social history and organization, New York history, the history of psychiatric nursing education, and public welfare."

This book is naturally of special interest to those connected with the New York Hospital and those interested in psychiatric hospitals. As a publicly available record, the advantage of such detailed local histories so greatly outweighs the occasional, unavoidable tedium of the story, that the matter does not seem to require further argument—the more such good local productions the better! E. K.

**WOMEN AND MEN.** By **AMRAM SCHEINFELD**, Author of "You and Heredity." Pp. 453. Illustrations by the Author. New York: Harcourt, Brace, 1944. Price, \$3.50.

THIS book in semi-popular style by an experienced writer in the field aims to help the two sexes understand themselves in relation to each other. The author first touches on Myths and Muddles arising from failures in understanding, then in the other 29 chapters, he pursues his theme of basic sex differences in logical order: first the seed, then first steps and puberty, with emphasis on the earliest years when developing sex differences are most significant; sickness; sex life; crime; labor, and so forth to the "marriage of tomorrow." Added to evidence of the lesser rôle of the male in procreation, he has added instances of greater female power of non-muscular kinds and of persistence in each sex of bisexual characteristics, all leading to the more important place occupied by woman in modern life. This same well-informed exposition of the overlapping behavior patterns of the two sexes should be profitable to the physician as well as to the discerning lay man. E. K.

**THE CHEMISTRY AND PHYSIOLOGY OF HORMONES.** Publication of the American Association for the Advancement of Science. Edited by FOREST RAY MOULTON. Pp. 243. Washington, D. C.: American Assn. Advanc. of Sci., 1944. Price, \$3.50 (\$4.00).

THIS is a Symposium volume of 17 papers presented during a 5 days, Research Conference at Gibson Island, Md., during 1943. The papers are reviews that were presented by selected active research workers, with modifications made as a result of discussions that ensued among those attending the conference. There are many charts and illustrations. Over 200 references are combined at the end of the book.

As a compilation of data and expression of modern concepts of the chemistry and physiology of hormones, the book presents desirable authoritative information about research aspects of endocrinology.

The pituitary receives greatest emphasis, the parathyroids are entirely omitted. I. Z.

### NEW BOOKS

*Penicillin and Other Antibiotic Agents.* By WALLACE E. HERRELL, M.D., M.S., F.A.C.P., Assistant Professor of Medicine, the Mayo Foundation, Univ. of Minnesota; Consultant in Medicine, Mayo Clinic, Rochester, Minn. Pp. 348; 45 figs.; 45 tables. Phila.: Saunders, 1945. Price, \$5.00.

*Transactions of the Association of American Physicians.* Fifty-eighth Session Held at Atlantic City, N. J., May 9, 1944. Vol. LVIII. Pp. 204. Phila.: Assn. of Am. Phys., 1944.

*Foster Home Care for Mental Patients.* By HESTER B. CRUTCHER, Director of Social Work, State of New York, Department of Mental Hygiene. Pp. 199. New York: Commonwealth Fund, 1944. Price, \$2.00.

*Fundamentals of Pharmacology.* By CLINTON H. THIENES, M.D., Ph.D., Professor and Head of the Department of Pharmacology, School of Medicine, Univ. of Southern California. Pp. 497. New York: Hoeber, 1945. Price, \$5.75.

*The Psychology of Women.* A Psychoanalytic Interpretation. Vol. II. Motherhood. By HELENE DEUTSCH, M.D., Associate Psychiatrist, Massachusetts General Hosp.; Lecturer, Boston Psychoanalytic Institute. Pp. 399. New York: Grune & Stratton, 1945. Price, \$4.50.

*Modern Psychiatry.* By WILLIAM S. SADLER, M.D., F.A.P.A., Consulting Psychiatrist to Columbus Hosp.; Consultant in Psychiatry, The W. K. Kellogg Foundation; Fellow of the American Psychiatric Assn.; Member of the American Psychopathologic Assn. Pp. 896. St. Louis: Mosby, 1945. Price, \$10.00.

*Ageing and Degenerative Diseases.* Edited by ROBERT A. MOORE, School of Medicine, Washington Univ. Vol. XI of Biological Symposia. A series of Volumes Devoted to Current Symposia in the Field of Biology. Edited by JAMES CATTELL. Pp. 242. Various tables and figs. Lancaster: Cattell Press, 1945. Price, \$3.00.

*Francois Magendie.* Pioneer in Experimental Physiology and Scientific Medicine in XIX Century France. By J. M. D. OLMSTED, Professor of Physiology, Univ. of California. With a Preface by JOHN F. FULTON. Illustrated. Pp. 290. New York: Schuman's, 1944. Price, \$5.00.

*The Chemical Formulary.* A Collection of Valuable, Timely, Practical Commercial Formulæ and Recipes for Making Thousands of Products in Many Fields of Industry. Vol. VII. Editor-in-Chief, H. BENNETT. Pp. 474. Brooklyn: Chemical Publishing Co., 1945. Price, \$6.00.

*Malaria, Primate.* By S. D. ABERLE, M.D. National Research Council, Division of Medical Sciences. Pp. 171. Issued by the Office of Medical Information (Under grant of the Johnson & Johnson Research Foundation), March, 1945.

*Public Medical Care.* Principles and Problems. By FRANZ GOLDMANN, M.D. Pp. 226. New York: Columbia Univ. Press, 1945. Price, \$2.75.

## NEW EDITIONS

- Diseases of the Nervous System in Infancy, Childhood, and Adolescence.* By FRANK R. FORD, M.D., Associate Professor of Neurology, The Johns Hopkins Univ. Second Ed. Pp. 1143; 164 ills., 22 charts, 14 tables. Springfield: Thomas, 1944. Price, \$12.50.
- Infants and Children. Their Feeding and Growth.* By FREDERIC H. BARTLETT, M.D., Attending Pediatrician, Babies' Hosp., New York City. New Ed. Pp. 428. New York: Farrar & Rinehart, 1944. Price, \$2.00.
- Essentials of Body Mechanics in Health and Disease.* By JOEL E. GOLDTHWAIT, M.D., F.A.C.S., LL.D., et al. With a Chapter on the Heart and Circulation as Related to Body Mechanics, by WILLIAM J. KERR, M.D., F.A.C.P. Pp. 337; 128 ills. Fourth Ed. Phila.: Lippincott, 1945. Price, \$5.00.
- Dietary of Health and Disease.* By GERTRUDE I. THOMAS, Assistant Professor of Dietetics, Univ. of Minnesota. Fourth Ed. Pp. 308; illustrated. Phila.: Lea & Febiger, 1945. Price, \$3.50.
- The Management of Obstetric Difficulties.* By PAUL TITUS, M.D., Obstetrician and Gynecologist to the St. Margaret Memorial Hosp., Pittsburgh; Secretary of the American Board of Obstetrics and Gynecology; Commander (MC), USNR, attached to Professional Division, Bureau of Medicine and Surgery, Navy Department, Washington, D. C. Third Ed. Pp. 1000; 426 ills. and 8 color plates. St. Louis: C. V. Mosby, 1945. Price, \$10.00.
- The Human Mind.* By KARL A. MENNINGER. Third Ed. Pp. 517; corrected, enlarged and rewritten. New York: Knopf, 1945. Price, \$5.00.
- The Basis of Clinical Neurology. The Anatomy and Physiology of the Nervous System in Their Application to Clinical Neurology.* By SAMUEL BROCK, M.D., Professor of Neurology, Coll. of Medicine, New York Univ. Second Ed. Pp. 393; 72 figs. Baltimore: Williams & Wilkins, 1945. Price, \$5.50.
- A Synopsis of Medicine.* By SIR HENRY LETHEBY TIDY, K.B.E., M.A., M.D., B.CH. (OXON.), F.R.C.P. (LOND.), Extra Physician to H. M. The King; Consulting Physician to St. Thomas's Hosp. Eighth Ed., revised and enlarged. Pp. 1215. Baltimore: Williams & Wilkins, 1945. Price, \$7.50.
- Textbook of Neuropathology.* By ARTHUR WEIL, M.D., Associate Professor of Neuropathology, Northwestern Univ. Med. School. Second Ed. Pp. 370; 289 ills. New York: Grune & Stratton, 1945. Price, \$5.50.

## NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMHAAER, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles, arranged alphabetically according to the name of the first author, and should be complete that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

For the balance of the war, 150 REPRINTS will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150.

# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

AUGUST, 1945

## ORIGINAL ARTICLES

### A COMPARISON OF THE BEHAVIOR OF MICROCRYSTALLINE SULFADIAZINE WITH THAT OF ORDINARY SULFADIAZINE IN MAN\*

BY JOHN G. REINHOLD, PH.D.

PRINCIPAL BIOCHEMIST, PHILADELPHIA GENERAL HOSPITAL

FRED. J. PHILLIPS, M.D.

ALFRED STENGEL FELLOW IN MEDICINE, PHILADELPHIA GENERAL HOSPITAL

HARRISON F. FLIPPIN, M.D.

VISITING PHYSICIAN, PHILADELPHIA GENERAL HOSPITAL

(With the technical assistance of LILLIAN POLLACK)

PHILADELPHIA, PA.

(From the Committee on Chemotherapy, Philadelphia General Hospital)

FREQUENTLY the need arises, particularly in the treatment of children, for administration of sulfonamides orally in a liquid form. It is not possible to obtain solutions of the more effective compounds, such as sulfadiazine, because of their low solubility in water. The sodium salts are soluble, but their solutions are not permanently stable. Suspensions of the ordinary crystalline material tend to settle out rapidly, and as is shown in this paper, are inferior in some respects. In contrast, microcrystalline preparations of sulfadiazine and sulfathiazole remain suspended for weeks or even longer, and thus appear capable of providing the required fluid dosage form.

Microcrystalline sulfonamides have shown differences from ordinary sulfonamides in both pharmacodynamic behavior and therapeutic activity.<sup>2,5,6,8,9</sup> In general, such differences suggest that in microcrystalline form the activity is enhanced, but the information available is limited, and it is desirable that further investigations be made.

The results of such studies are presented in this paper. The rate of absorption and urinary excretion after ingestion of microcrystalline sulfadiazine† has been compared with that observed when ordinary

\* This work was aided by a grant from the Research Fund for Infectious Diseases, University of Pennsylvania, Philadelphia.

† Microcrystalline sulfadiazine measures  $1 \times 1 \times 3$  microns and is approximately 1/350 of the mass of ordinary sulfadiazine crystals.

sulfadiazine was administered. The effects of food and of sucrose and flavoring material on the rate of absorption were also studied. Concentrations established in blood when patients received microcrystalline sulfadiazine have been compared with those obtained when ordinary sulfadiazine was used. Finally, the therapeutic activity of sulfadiazine in these two forms has been evaluated.

**Materials and Methods.** For the comparison of the behavior of microcrystalline sulfadiazine with that of ordinary sulfadiazine convalescent adult patients of the Medical Wards of the Philadelphia General Hospital served as subjects. The various preparations were examined under conditions closely comparable, with respect to type of subject, time, dosage, etc. In most instances, the same individual served as subject for comparison of different preparations. Each was given 3 gm. of the preparation being used, body weight being disregarded. Blood and urine specimens were collected at the times shown in the graphs; serum was used for the sulfadiazine determinations. These were made by the method of Bratton and Marshall<sup>1</sup> with the aid of a Klett-Summerson photoelectric photometer. The term "ordinary" sulfadiazine has been employed in this paper to distinguish the usual crystalline sulfadiazine, either in U.S.P. tablet form or as suspensions in water or sucrose, from the microcrystalline preparation.

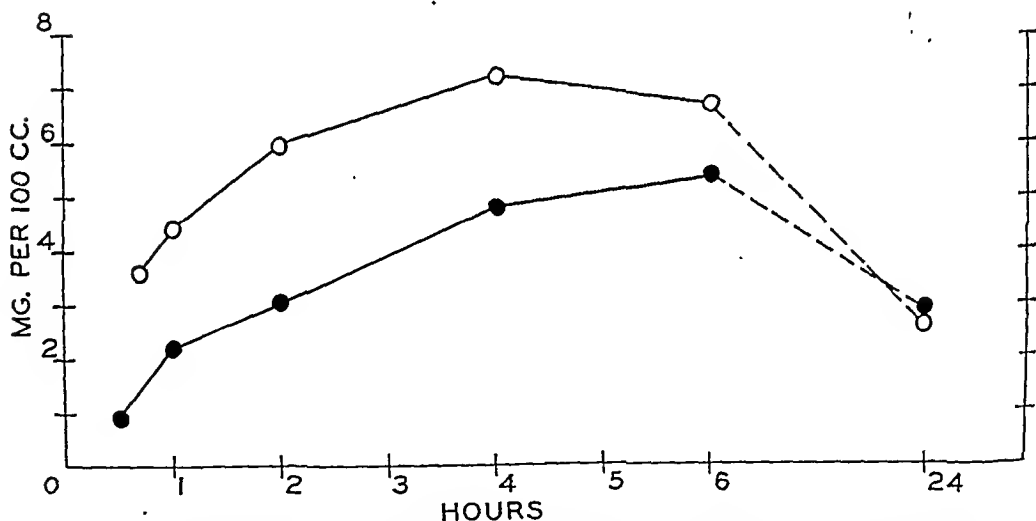


FIG. 1.—Response to microcrystalline sulfadiazine, compared with that to ordinary sulfadiazine as shown by serum sulfadiazine concentrations. Average serum sulfadiazine concentration at timed intervals after ingestion. Circles: all microcrystalline preparations, 36 subjects. Solid circles: ordinary sulfadiazine preparations, 30 subjects. Each subject received 3 gm.

**Results.** Figure 1 shows the trend of the concentrations of sulfadiazine in serum, following ingestion of microcrystalline sulfadiazine (upper curve) in contrast to that seen when ordinary sulfadiazine (lower curve) was ingested. When the former was used, the concentrations in serum are distinctly higher during the first 6 hours. The difference is greatest in the earlier specimens, then gradually diminishes following the 4th hour. The difference\* was still significant at

\* Differences were tested by Fisher's T test, as described by Goulden.<sup>4</sup> At the 6th hour,  $p < 0.05$  and  $> 0.02$ .

the 6th hour, but extrapolation of the curves indicates that beyond this point the two would meet and probably intersect. At 24 hours the concentrations were the same.

Since the preparation of sulfadiazine microcrystals used (Eskadiazine)\* contained sucrose and essential oils, it was thought important to evaluate the contribution of these substances to the differences between the sulfadiazine in micro- and ordinary crystalline form. For this purpose, a separate group of 7 subjects was given microcrystalline sulfadiazine (Fig. 2) suspended in water, and without the flavoring material. The response did not differ from that of the principal group of 17 subjects.

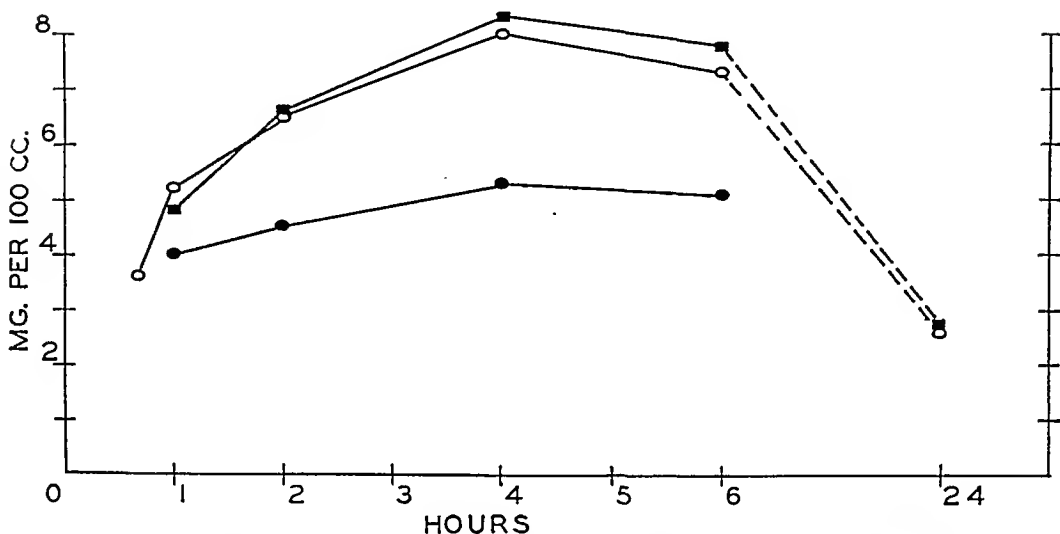


FIG. 2.—Response to microcrystalline sulfadiazine as shown by serum sulfadiazine. Effect of flavoring material and of fasting. Ovals: sucrose and essential oils present, non-fasting, 17 subjects. Solid rectangles: suspension of microcrystals in water, non-fasting, 7 subjects. Solid ovals: sucrose and essential oils present, fasting, 12 subjects.

However, fasting did exert a definite influence. Subjects who had taken their last meal 16 hours before responded with a much smaller rise in serum sulfadiazine concentration. Two hours after ingestion of the flavored microcrystalline material, the average concentration was significantly less than when the subjects had partaken of food within the preceding 2 or 3 hours. The difference persisted during the 6 hour period of observation.

The marked effect of fasting on uptake of sulfadiazine administered as microcrystals was not observed when ordinary preparations of sulfadiazine were used (Fig. 3). Likewise, inclusion of sucrose in amount sufficient to prevent settling of the crystals (about 20%) together with essential oils as flavoring, had no effect. The slower more gradual rise in serum sulfadiazine when sulfadiazine tablets were given was at first attributed to delay in disintegration of the tablet.

\* This and other sulfadiazine preparations used were supplied through the courtesy of Smith, Kline & French Laboratories, Inc., Philadelphia.

However, administration of a suspension of crushed tablets failed to alter the response.

The individuals receiving preparations of microcrystals excreted more sulfadiazine in urine during the first 6 hours than did those who received plain sulfadiazine (Fig. 4). The difference was statistically significant. In subsequent periods there were smaller differences which however were not significant. The average total output in 48 hours of 11 subjects of the group receiving microcrystals was 1.999 grams and that of 10 subjects who received sulfadiazine was 1.699 grams. This difference likewise was not significant.

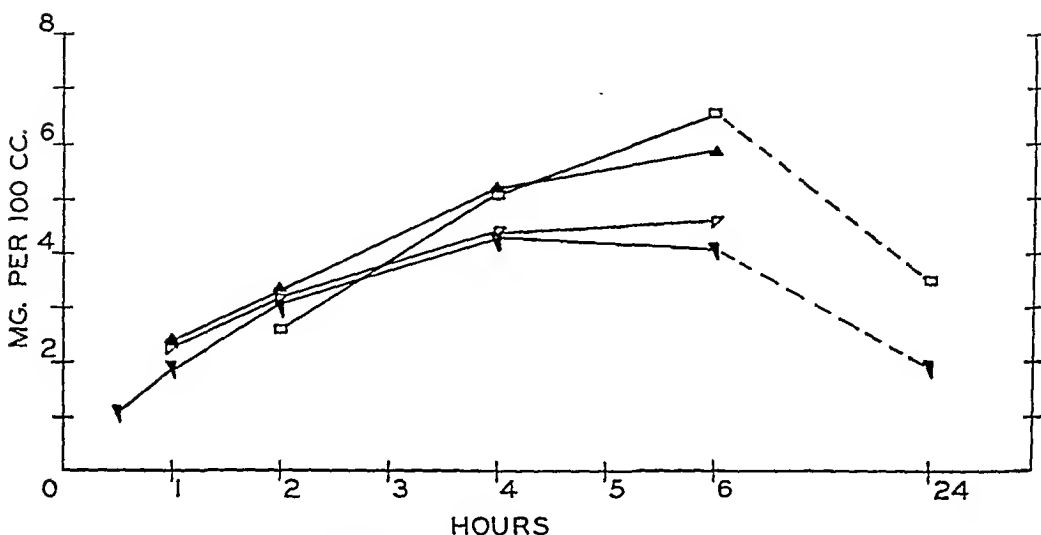


FIG. 3.—Effect of fasting and flavoring material, together with a comparison of tablets and suspensions of sulfadiazine on sulfadiazine concentrations in serum. Rectangles: sulfadiazine tablets, non-fasting, 9 subjects. Solid upright triangles: sulfadiazine suspension, non-fasting, 8 subjects. Open triangles: sulfadiazine suspension with added sucrose, fasting, 6 subjects. Solid inverted triangles: sulfadiazine suspension with added sucrose, non-fasting; 7 subjects.

It will be seen that the standard errors (Fig. 4) of the averaged urine excretions were much smaller in the group receiving microcrystalline preparations than in those receiving plain sulfadiazine. Likewise, there was less variation in the individual serum sulfadiazine curves when microcrystalline preparations were ingested. This more uniform response when microcrystals were administered was a consistent finding. The same individuals to a predominant extent made up the two groups; thus individual differences were not the cause.

Forty-five patients receiving microcrystalline preparations (4 gm. per day at 6 hour intervals) for periods up to 10 days showed an average sulfadiazine concentration of 9.3 mg. per 100 cc. serum. An entirely comparable group of 45 receiving sulfadiazine in the same amount, either as tablets or as a suspension in sucrose solution with other flavoring material, yielded an average of 10 mg. per 100 cc. The difference is not statistically significant.

Observation of the therapeutic action of microcrystalline sulfadiazine in 75 patients suffering from pneumonia showed no evidence of decreased therapeutic effectiveness or of increased toxicity, as compared with ordinary sulfadiazine.<sup>3</sup>

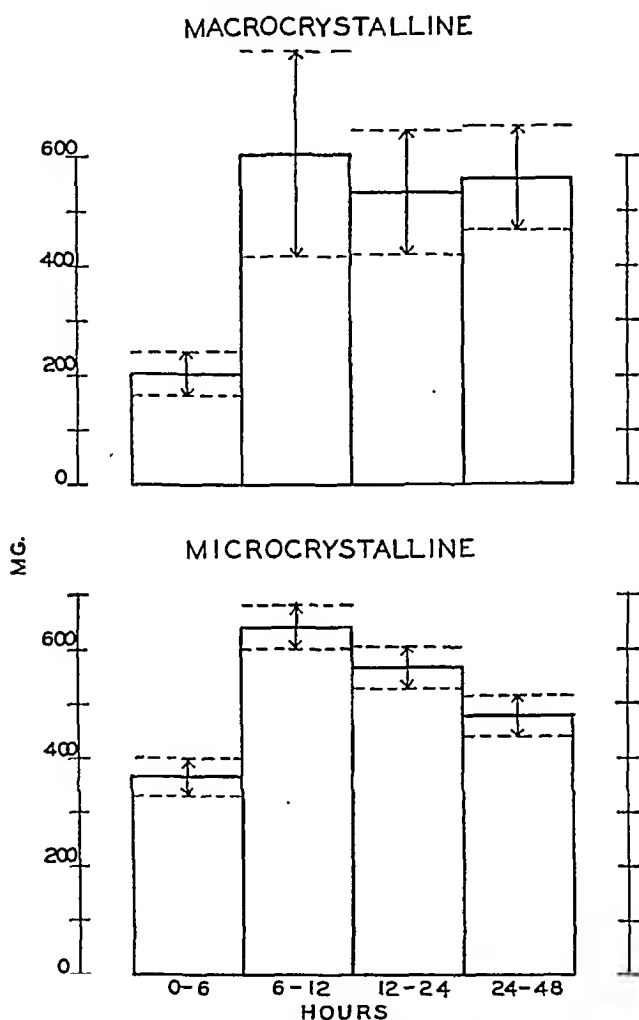


FIG. 4.—Excretion of sulfadiazine in urine after ingestion of microcrystalline preparations compared with ordinary sulfadiazine preparations. The dotted lines and arrows show the standard errors of the means.

**Discussion.** The more rapid rise in concentrations of sulfadiazine in serum and the more rapid excretion in urine during the 1st hours following ingestion of microcrystalline sulfadiazine must be the result of an increased rate of absorption when in this form. The most plausible explanation is that microcrystalline material remains in suspension in the stomach and consequently is moved toward the pylorus and discharged into the duodenum sooner than is ordinary sulfadiazine. The latter settled from suspensions in water rapidly and thus could easily deposit in the body of the stomach, with the result that its



movement toward the pyloric antrum would be delayed. Suspensions of ordinary crystals in sucrose were more permanent but their effect was negligible, again because dilution of the sucrose in the stomach would permit precipitation.

Accelerated absorption of microcrystalline sulfadiazine when the stomach contains food probably is the result of increased peristaltic activity causing more rapid movement of the suspended material into the pylorus. Absence of a similar effect of food when ordinary crystals are ingested would likewise be the result of failure of such crystals to remain suspended as the contents of the stomach became liquefied. It should be noted that Peterson and Finland<sup>7</sup> observed higher concentrations of sulfadiazine in blood when their subjects had eaten breakfast than in fasting subjects. The difference observed was quite similar to that seen in the group described by us who had ingested microcrystalline sulfadiazine. We failed to find any indication of a similar effect in our subjects when ordinary sulfadiazine was investigated. No evidence exists that absorption of sulfadiazine occurs in the stomach. Even if it were physiologically feasible, the solubility in acid solutions is so very low as to preclude any appreciable contribution to the serum sulfadiazine concentration from this source.

Another possible explanation for the more rapid uptake of sulfadiazine in microcrystalline form is a difference in rate of solution when in contact with alkaline secretions in the intestine. However, experiments in which sulfadiazine, either in ordinary or microcrystalline form, was exposed briefly to solutions of sodium bicarbonate at pH 8 failed to show a difference between the two with respect to the amount dissolved.

**Summary** 1. Patients receiving by mouth suspensions of microcrystalline sulfadiazine (3 gm.) showed significantly higher concentrations of sulfadiazine in serum during the first 6 hours following its ingestion than did those who received ordinary sulfadiazine.

2. The excretion of sulfadiazine in the urine of those receiving microcrystalline material was likewise significantly higher during this period. These observations indicate that microcrystalline sulfadiazine is absorbed more rapidly than is ordinary sulfadiazine.

3. The presence of sucrose or of flavoring material had no influence on the rate of absorption of microcrystalline sulfadiazine or ordinary sulfadiazine.

4. In fasting subjects, the rate of absorption of microcrystalline sulfadiazine was decreased, but remained greater than that of ordinary sulfadiazine whether fasting or after meals. No such effect of fasting was observed in subjects given ordinary sulfadiazine.

#### REFERENCES

1. BRATTON, H. C., and MARSHALL, E. K., Jr.: *J. Biol. Chem.*, **128**, 537, 1939.
2. CHAMBERS, L. A., HARRIS, T. N., SCHUMAN, F., and FERGUSON, L. K.: *J. Am. Med. Assn.*, **119**, 324, 1942.
3. FLIPPIN, H. F., SCHWARTZ, L., and DOMM, A. H.: *J. Am. Med. Assn.*, **121**, 230, 1943.
4. GOULDEN, C. H.: *Methods of Statistical Analysis*, New York, 1939.

5. HARRIS, T. N.: J. Am. Med. Assn., 121, 403, 1943.
6. PEARCE, A. E., REINHOLD, J. G., FELDMAN, R. P., and BOWER, J. O.: Surgery, 17, 351, 1945.
7. PETERSON, O. L., and FINLAND, M.: AM. J. MED. SCI., 204, 581, 1942.
8. ROSE, S. B.: Personal communication.
9. SILCOX, L. E., and SCHENCK, H. P.: Arch. Otolaryngol., 36, 171, 1942.

## PENICILLIN—ITS PRESENT STATUS IN THE TREATMENT OF INFECTIONS\*

### THE NATHAN HATFIELD LECTURE XXIX

BY CHESTER S. KEEFER

BOSTON, MASS.

(From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine)

SEVERAL weeks ago, a young woman was admitted to our Clinic at the Evans Memorial complaining of chills and fever. She had been well until 3 days before admission when there was a sudden departure of health. Upon examination, it was found that she had high fever, pain in the right ankle joint, and the physical signs of a bilateral bronchopneumonia. The blood culture showed numerous colonies of *Staphylococcus aureus*. She was placed on penicillin therapy at once. Within the first 2 days the temperature was reduced to a lower level, but she developed a right-sided hemiparesis with aphasia, and the signs of an acute arthritis of the right ankle joint. Gradually over a period of 3 weeks the temperature returned to normal, the other signs of infection disappeared and she made a complete recovery with the exception of a slight weakness of the right arm. The course of this patient's illness illustrates what can be accomplished in 90% of all cases of *S. aureus* infections with bacteremias when penicillin is given in adequate amounts for a sufficiently long period of time. When one recalls that the fatality rate in this disorder is usually between 50% and 75% without penicillin, it is plain that penicillin has completely changed the outlook in this group of infections. But this is not all. It can be said without reservation that penicillin is the most remarkable chemotherapeutic agent that has been discovered up to the present time. When one makes such a statement it is well to document it. In the first place, it is a substance of extremely great antibacterial power. One mg. of crystalline penicillin is capable of inhibiting the growth of staphylococci in 82.5 liters of broth. It is non-toxic in maximum therapeutic doses in man. It is highly effective against a wide variety of microorganisms of the gram-positive group. It is effective in both gonorrhea and syphilis, the two commonest genito-infectious diseases. It is responsible for the reduction of the fatality rate in more diseases than any other chemotherapeutic agent; it

\* The work in preparing this review was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Massachusetts Memorial Hospitals, Robert Dawson Evans Memorial, Department of Clinical Research and Preventive Medicine.

shortens the clinical course of many infectious disorders, and it saves many days of illness and disability. When one realizes that this can be accomplished by an agent that destroys bacteria and other microorganisms such as the *Treponema pallidum* without injuring the tissues of the host, it deserves to be called remarkable. No other known agent can do as much.

There are many fascinating historical events to be recorded in the development of penicillin. At this time 3 years ago, there was not enough penicillin in this country to treat a single patient. Two years ago, only 100 patients had received treatment. Today there is enough penicillin being produced in this country alone to supply our Armed Services and those of our Allies, and a moderate amount for civilians. This progress has been due to the combined efforts of many groups working in universities, hospitals, in industry and in government.

Tonight I want to review for you the present status of penicillin treatment in the common infections.

**Salts Used and Routes of Administration.** First of all, I shall make a few remarks concerning the best route of administration. There are 2 salts of penicillin available for clinical use, the sodium and the calcium salts. They are both equally effective therapeutically and they can both be used interchangeably. The commonest route of administration is the intramuscular, and it is the route of choice. Injections may be given intermittently or continuously. It may also be given intravenously, and topically into the serous cavities, joint cavities, or into the subarachnoid space.

In an attempt to delay absorption from local deposits in the muscles, penicillin has been combined with beeswax and peanut oil or with gelatin and vasoconstrictor drugs. These methods show considerable promise and when the details have been worked out, the use of such a method will undoubtedly reduce the number of injections required to maintain adequate concentrations of penicillin in the blood and tissues.

When penicillin is given by mouth, the coefficient of absorption is small and varies between 2 and 10%. When large amounts are given by this route and at frequent intervals in oil, or in buffers such as sodium citrate, a sufficient amount is absorbed to influence the course of infections. In the case of gonorrhea or lobar pneumonia, recovery may be observed following the use of 5 to 10 times as much as is needed when penicillin is given parenterally. At present the use of penicillin by mouth is wasteful, uncertain and expensive, when compared to other routes of administration.

**Dosage.** It is difficult, and indeed impossible, to make any absolute rules concerning the necessary dosage of penicillin that will be universally applicable. The daily and total dose will depend upon the type of infection, its location, the presence of bacteremia, the age and the clinical condition of the patient and the course of the disease.

For example, it is a well-established fact that there is a wide variation in the susceptibility of various organisms to penicillin. The gonococcus is the most sensitive organism so that between 50,000 and

150,000 units will cure 98% of cases of gonorrhea within 24 hours. The hemolytic *Staphylococcus aureus* is more resistant, so that between 100,000 and 200,000 units a day for 1 to 3 weeks or longer may be required. In the case of bacterial endocarditis due to *Streptococcus viridans*, at least 300,000 units daily for a period of 14 to 21 days may be considered a minimum dose.

One of the greatest difficulties in assessing dosage is the lack of signs of toxicity so that the maximum tolerated dose is not known. Conversely the minimum effect dose is difficult to define in all cases. The most reliable guides to dosage are the type of specific organism and the response of the patient to treatment.

**Generalized Infections With Bacteremia.** Generalized infections with bacteremia due to susceptible organisms, such as the *S. aureus*, *Strep. hemolyticus* or the pneumococcus, respond in a most favorable manner to penicillin. The outlook in individual cases will depend to some extent upon such factors as the source of the primary infection, the age of the patient, the period at which treatment is begun and, in some instances, the accessibility of the infection to surgical treatment. The best results have been obtained in young individuals who have a recent infection and who have been given active and intensive treatment with 120,000 to 240,000 units a day. Less favorable results have been seen in elderly patients with overwhelming infections, bacterial endocarditis, meningitis, or when the infection is associated with some complicating debilitating disease.

In the case of staphylococcic bacteremia, the overall fatality rate has been reduced to within 10 to 20%. It has been lowest in young persons with osteomyelitis (10%) and highest in those with bacterial endocarditis (75%).

In all cases with bacteremia the treatment should be continuous for 2 to 3 weeks and enough penicillin should be given daily to bring the infection under control.

**Infections of the Meninges.** *Meningococcus Meningitis.* Sulfadiazine continues to be the drug of choice in the treatment of meningococcic meningitis. While penicillin is effective in controlling this disease, the response is slower than following the sulfonamides, and it continues to be necessary to give penicillin both systemically and intrathecally. In cases failing to respond to the sulfonamides within a period of 24 to 48 hours with adequate treatment, penicillin should be started at once. Penicillin is the drug of choice in the treatment of all infections of the meninges due to the pneumococcus, staphylococcus and the hemolytic streptococcus. Treatment should be started as soon as the diagnosis is established, and all foci of infection in the neighborhood which can be drained surgically should be attacked at the same time. This is especially true when there is an associated mastoiditis or lateral sinus thrombosis.

*Pneumococcus Meningitis.* Pneumococcus meningitis is always a serious disease. Before the days of the sulfonamides it was invariably fatal. Now a certain number of patients, that is, between 40 and 50%, recover following the use of either the sulfonamides or penicillin.

There is some evidence that the combination of sulfadiazine and penicillin may be better than either drug alone.<sup>1</sup>

One of the reasons that pneumococcus meningitis is such a serious disease is that it is frequently a metastatic lesion following pneumococcus lobar pneumonia with or without an associated bacterial endocarditis. In other cases it follows craniocerebral injuries, otitis media and/or mastoiditis or suppurative sinusitis of the ethmoid or sphenoid cells. Another reason for the severity of this infection is that it tends to produce hydrocephalus and an encephalitis which may lead to cerebral atrophy and profound neuropsychiatric disturbances.

**Otitis Media and Mastoiditis.** Patients with otitis media and mastoiditis respond to penicillin treatment most favorably. In the case of mastoiditis, simple mastoidectomy followed by closure of the incision with the insertion of a small catheter so that penicillin can be instilled into the cavity for 3 or 4 days is the method of choice, as demonstrated by Johnson, Weinstein and Spence.<sup>2</sup> Under these conditions healing takes place rapidly and the postoperative course is greatly shortened.

**Tonsillitis.** Tonsillitis resulting from hemolytic streptococcal infection responds very promptly to the use of penicillin. Treatment should be continued for at least 5 to 7 days in order to prevent relapses. One of the striking features following the treatment is the rapid decrease in the number of organisms in the throat. Indeed, it is often difficult to recover streptococci from the local focus of infection 24 or 48 hours after treatment is started. If, however, there is an interruption of treatment, there may be relapses of infection and organisms will reappear in great numbers in the throat. For this reason, it is essential that the treatment be continued for at least several days after all signs of acute infection have subsided.

**Pneumococcus Pneumonia.** The pneumococcus is extremely susceptible to the action of penicillin *in vitro* and when patients with pneumococcus lobar pneumonia receive penicillin, the outcome is extremely favorable. Tillett, Cambier and McCormack<sup>3</sup> have recorded a fatality rate of only 6.5% in 106 cases, and in all of the fatal cases there were complicating factors. Meads, Harris and Finland<sup>4</sup> record favorable results in cases in which the sulfonamides had previously failed to control the infection. The latter group of investigators found that penicillin was equally effective in the patients who had received it alone or in those who had failed to respond to the sulfonamides.

There are a number of points worth commenting on with respect to the treatment of pneumococcus lobar pneumonia with penicillin. When patients are treated early in the course of their disease, that is, within the first 24 or 48 hours, there is usually a decrease in the temperature and pulse rate within the first 24 to 48 hours and preceding these objective signs, the patients feel improved subjectively.

Bacteremia, if present, disappears promptly, usually following the first injection, and purulent complications following the use of penicillin are exceedingly uncommon. They were not observed by Meads, Harris and Finland in any of their cases.

The dosage and duration of treatment will vary from one patient to

another, depending upon the clinical response and the severity of the infection. In some mild cases, a satisfactory response has been observed following 60,000 to 80,000 units a day for 2 days, given in doses of 10,000 units every 3 or 4 hours. In other cases, the equivalent of at least 15,000 units every 2 hours for the first 12 or 24 hours, after which longer intervals or smaller amounts may be used for another 2 or 3 days. It is wise and sound practice to continue treatment for 2 or 3 days after the temperature has reached normal in order to avoid relapses which may be observed if treatment is stopped abruptly after the first 48 or 72 hours. Certainly the total dosage during the first 24 hours must be gauged by the condition of the patient and his response to the treatment.

In attempting to assess the conditions in which the sulfonamides or penicillin should be used in the treatment of pneumococcus lobar pneumonia, it is not possible at the time of this writing to make any definitive rules. Both agents are effective. However, the sulfonamides can be given by mouth and penicillin must be given parenterally. This may be a consideration in some cases. However, it is well to recall that penicillin is non-toxic and that the sulfonamides may cause side reactions. In general, it can be said that penicillin is the drug of choice in: (1) all patients who have failed to respond to the sulfonamides after 24 hours of treatment; (2) all patients with a persistent bacteremia; (3) all patients who show a spread of the process; (4) all patients who develop any signs of sulfonamide intoxication or renal irritation; and (5) all patients who have leukopenia or who develop auricular fibrillation, delirium tremens or other complications during the infection.

It is well to start with penicillin when the patient is acutely ill or has developed a shock-like state, or when he has some complicating disease such as renal, hepatic, or cardiac disorder, or when there is leukopenia or a history of sensitivity to the sulfonamides.

In brief, it can be said that penicillin can be given with greater safety than sulfadiazine and with the same good results. It will gradually become the drug of choice in the treatment of all cases of pneumonia.

**Subacute Bacterial Endocarditis.** When subacute bacterial endocarditis due to the non-hemolytic streptococcus was first studied, the results of penicillin treatment on the clinical course were discouraging. In some cases, when 30,000 to 60,000 units were given daily, the blood was cleared of organisms and the temperature was reduced for the period of treatment. However, the course of the disease was not otherwise influenced and when the drug was withdrawn, the bacteremia recurred and progressive signs of infection ensued. It is now known that these results were due to an inadequate amount of penicillin. When larger amounts of penicillin are given for longer periods of time, that is, 200,000 or 300,000 units a day for at least 3 weeks, there will be a clinical arrest of the disease varying from 1 to 10 months in about 55% of cases (Fig. 1). A certain number of patients will die before adequate treatment as described above has been completed. Death



obtained with penicillin alone and no anticoagulant such as heparin is necessary.

Following a clinical arrest, the patient may return to apparently normal health in that the symptoms and signs of infection are absent. Some patients have recurrences as long as 6 to 9 months after treatment. A number of patients die of cardiac insufficiency without signs of active infection.

**Acute Osteomyelitis.** Evidence is now accumulating that acute osteomyelitis can be treated satisfactorily without surgical intervention when the therapy is started early in the course of the disease and before abscesses of the soft parts or extension of the infections of the joints has occurred. Penicillin must be given in amounts varying from 120,000 to 250,000 units a day and continued for a period of 2 to 3 weeks until all clinical symptoms and signs of infection have disappeared. Since there is a lag between the clinical signs of infection and the development of definite roentgenologic changes in the bone, one is not surprised to find that destruction of the bone is observed some time after all signs of infection have disappeared. Under these conditions, the lesions in the bone frequently recalcify and complete healing takes place without incision and drainage.

When the infection has spread into a neighboring joint, it is desirable to perform whatever surgery is necessary to make possible the local instillation of penicillin into the involved joint at least once or twice a day. In all cases of acute osteomyelitis in which recovery has taken place without surgical treatment, the patient should be followed carefully over a period of several months in order to be certain that relapses or recurrences do not occur. In a few cases it may be necessary to drain local abscesses in bone some weeks after the acute infection has subsided. In occasional cases that have been treated very early, no signs of bone destruction have ever developed in the roentgenograms.

The treatment of osteomyelitis of the facial bones with penicillin has been followed by excellent results, as reported by Kirby and Hepp.<sup>5</sup> When sequestra were present, surgical treatment in addition to the use of penicillin was necessary to effect complete recovery.

In the case of chronic, hematogenous and traumatic osteomyelitis, Anderson, Howard and Rammelkamp<sup>6</sup> have found that when sequestra are present it is necessary to remove them surgically in order to obtain satisfactory healing. These physicians were able to report an arrest of the disease with the disappearance of all local and constitutional signs of active infection in 70% of their patients with chronic osteomyelitis. Prolonged treatment varying from 2 to 6 weeks was found to be necessary in order to obtain the best results. Treatment has to be repeated when relapses occur. Primary closure of wounds after sequestrectomy, together with the local administration of penicillin, greatly shortens the recovery period. In brief, the treatment of acute and chronic osteomyelitis should be designed to control the infection as rapidly as possible. If dead or necrotic tissue is present, or if abscesses in the soft parts or in the joints have appeared, it is necessary



to use good surgical management as well as penicillin if the best results are to be obtained.

**Infections Due to Clostridia.** *Gas Gangrene.* The best results in the treatment of gas gangrene follow the use of antitoxin, penicillin, and surgical removal of all necrotic and damaged tissue. If gas gangrene tends to develop in patients who have had injuries to the bone and soft parts with an interruption of the blood supply to the affected part, it is only natural that a certain number of patients will not respond to any form of treatment unless all of the ischemic and damaged tissue has been removed. Jeffrey and Thomson,<sup>7</sup> in a study of 33 cases of gas gangrene treated with penicillin, reported a fatality rate of 36.4%. They emphasize, as has already been remarked, that adequate surgical removal of all necrotic and devitalized tissue is the most essential of therapeutic procedures in the management of gas gangrene. Five of their patients were seen late in the disease when surgical treatment was not possible. All of these patients died in spite of intensive treatment with penicillin. These physicians recommend a dosage of 15,000 units every 3 hours for 3 to 4 days for the control of infection in cases in which all the infected tissue can be removed surgically. When this is not possible, it is desirable to continue treatment for 5 to 10 days. They express the opinion that when patients are treated early and adequate surgery is employed, penicillin and antitoxin will reduce the fatality rate in battle casualties to the neighborhood of 20%. Cutler and Sandusky<sup>8</sup> reported their experience with the treatment of 7 patients with gas gangrene, 6 of whom recovered. It is significant that in 5 of their patients, gas gangrene developed while the patients were receiving prophylactic penicillin therapy. Following the removal of diseased tissue, all of these patients recovered.

**Gonococcic Infections.** Of all the organisms that are susceptible to penicillin, the gonococcus is the most sensitive. It is now well established that about 98% of all gonococcic infections of the lower genital tract, either in men or women, can be cured by the administration of a total of 100,000 units of penicillin over a 24-hour period. The remaining 2% who fail to respond to the first course frequently respond to more intensive and prolonged treatment. No proved cases of penicillin-resistant gonorrhea have yet been encountered.

Gonococcic infections complicated by arthritis, prostatitis, salpingitis, epididymitis, or endocarditis, require much more prolonged treatment. Early and intensive treatment in all of these infections is advisable.

**Syphilis.** Following the report of Mahoney and his associates<sup>9</sup> in October 1943, intensive studies of the treatment of early syphilis, neurosyphilis and congenital syphilis have been carried out by a group of coöperating clinics reporting to the Penicillin Panel of the Subcommittee on Venereal Diseases of the National Research Council, and coöperating with the Committee on Medical Research of the Office of Scientific Research and Development. Final evaluation of the results will, of course, not be possible for several years. Preliminary reports indicate that a course of 60 injections of 20,000 units each,

given intramuscularly at 3-hour intervals for  $7\frac{1}{2}$  days, probably represents the minimum dosage schedule that will be effective in controlling primary and secondary syphilis. In some patients who relapse after this schedule of treatment, more prolonged and intensive treatment may be necessary. Not enough time has elapsed, and too few patients with neurosyphilis have been treated for a sufficiently long period of time to make any statement concerning the results that might be anticipated. There is some evidence to suggest that the results in the treatment of neurosyphilis are not as striking as those of early syphilis. Late cutaneous and osseous syphilis apparently respond promptly to penicillin treatment. So far, no reports are available on the action of penicillin in latent syphilis. Some cases of congenital syphilis have been treated in which good early results have been obtained.<sup>10</sup> It is agreed by all who are investigating this problem, that penicillin in the treatment of syphilis is still in the stage of preliminary investigation, and no definite schedule of treatment can yet be recommended for routine therapy.

During the treatment of syphilis with penicillin, Herxheimer reactions have occurred with considerable frequency. These are characterized by fever, malaise, headache, intensification of the eruption if one is present, or painful swelling of the primary lesions and the regional lymph nodes. These reactions subside within 24 hours and are not contraindications to continuing treatment.

**Toxic Reactions.** It has already been stated that penicillin is a non-toxic drug. There are, however, certain side reactions which may be observed which require comment. So far, no permanent harmful effects on any of the systems of the body have been recorded.

About 2 to 5% of patients develop *urticaria*. The urticaria may appear on the 1st day of treatment, or it may not appear until after treatment has been completed. When it develops, it is commonly seen during the 2nd week of treatment. In a few instances it may be quite severe and extensive, but in most cases it is mild and frequently disappears even though treatment is continued. When penicillin is readministered at a later date to a patient who has developed urticaria during the previous course of treatment, there may be a reappearance of the eruption. Urticaria is not regarded as a contraindication to continuing treatment or to readministration of the drug at a later date in most cases. In rare instances it may be advisable to stop treatment, especially if the discomfort is severe.

Occasional attacks of *vesicular eruptions* have been noted and we have seen one severe rash of this type appearing within 24 hours after the beginning of treatment, especially in areas where there was a severe ringworm infection 4 years previously.

*Pain* on intramuscular injection is encountered with varying frequency, depending upon the presence of impurities in the penicillin. The higher the potency of the penicillin, the less local discomfort there may be.

*Thrombophlebitis* of the veins at the site of injection may occur, especially in patients who are receiving continuous intravenous treat-

ment. Thrombophlebitis is associated in some instances with chills and high fever. When this occurs, it is wise to change from intravenous to intramuscular injections. All preparations of penicillin which are now distributed are tested for the presence of pyrogenic agents. The febrile reactions due to impurities that were occasionally encountered in the early days of developing penicillin are no longer seen. Drug fever, analogous to that seen in sulfonamide therapy, has not been reported. Occasionally patients may develop low grade fever after the clinical signs of infection have disappeared, and this subsides completely with the discontinuance of penicillin.

Occasional patients will develop *abdominal cramps* with or without *diarrhea* following penicillin, and *nausea* and *vomiting* have been observed in a few patients. The maximum therapeutic dose of penicillin that can be given safely in man has not yet been determined. It is known that doses as large as 4 million units a day have been given in 1 or 2 instances without ill-effect.

At present there are no known contraindications to the administration of penicillin, although there may be reason for giving small initial doses to patients with cardiovascular extragenital syphilis. As far as is known, penicillin is not incompatible with any other drug or article of diet.

**Miscellaneous Infections.** A large group of miscellaneous infections have received treatment with penicillin with promising results. In most instances the number of cases so treated has not been large, so that final assessment of its value cannot be made. However, patients with *actinomycosis* have been improved following treatment, and especially those cases in which it is possible to remove infected tissue surgically, or in those instances in which there is a superinfection due to the *S. aureus*. *Anthrax*, with or without bacteremia, responds promptly to penicillin, and a few cases of yaws and rat-bite fever due to *Streptobacillus moniliformis* have been treated with results suggesting that penicillin is a potent agent in these disorders.

Penicillin is active *in vitro* against *Corynebacterium diphtheriae*; a few cases of clinical diphtheria have been treated with a combination of antitoxin and penicillin with results that are difficult to evaluate. Penicillin will not replace antitoxin and should not be used *in lieu* of antitoxin. The supplementing of antitoxin with penicillin in cases of laryngeal diphtheria or diphtheria gravis may prove to be valuable, although the evidence to support this procedure remains to be accumulated. The treatment of diphtheria carriers with penicillin has not met with permanent success.

The position of penicillin in the treatment of chronic paranasal sinusitis, chronic infections of the ears, nose and throat, remains to be determined. The same is true with gingivitis and stomatitis caused by the Vincent organism.

**Prophylactic Use of Penicillin.** White and associates<sup>11</sup> have demonstrated that when penicillin is administered intramuscularly for 1 week prior to lobectomy or pneumonectomy and followed by continuation of penicillin treatment after operation, the incidence of postoperative

empyema is greatly reduced. Penicillin will perhaps not decrease the number of infections in wounds when it is not combined with adequate surgical treatment.

**Penicillin Failures.** No discussion of penicillin would be complete without saying something about the cases in which penicillin fails to influence the course of the disease. The largest group, of course, includes those cases of infection due to microorganisms which are not susceptible to the action of penicillin such as those listed in Table 1:

TABLE 1

Typhoid—paratyphoid	<i>B. pyocyaneus</i>
Dysentery (several varieties)	<i>Br. melitensis</i> (undulant fever)
<i>E. coli</i>	<i>P. tularensis</i> (tularemia)
<i>H. influenza</i>	<i>B. friedländer</i>
<i>B. proteus</i>	

The next large group are those disorders in which penicillin has been shown to be ineffective as listed in Table 2:

TABLE II

Tuberculosis	Pemphigus
Poliomyelitis	Toxoplasmosis
Hodgkin's disease	Blastomycosis
Histoplasmosis	Coccidiomycosis
Moniliasis	Acute rheumatic fever
Malaria	Virus infections
Cancer	Acute and chronic leukemia
Lupus erythematosus, diffuse	Ulcerative colitis
Non-specific iritis and uveitis	Infectious mononucleosis

In general it can be said that there is a fairly good correlation between the sensitivity of the infecting strain of microorganism and the clinical amenability to treatment, so that when the treatment appears to fail it may be due to inadequate daily dosage or to treatment of only a few days duration. The treatment may be started too late in the course of an infection, or there may be an overwhelming infection even with a sensitive strain.

In the case of wound infections, penicillin may fail in its function when débridement is incomplete, or when necrotic tissue or foreign bodies are present.

In our experience the development of increased resistance of microorganisms to penicillin plays little if any rôle in the failure of infections to respond to its action. While we can demonstrate a change of sensitivity in some strains of *S. aureus* during treatment when they are tested *in vitro*, the evidence is far from convincing that this phenomenon plays a dominant rôle when a regression of signs of infection fails to occur. The reason for this statement is that there are usually other factors present which influence the outcome. This is especially true when the resistance to penicillin increases in organisms in empyema cavities and in chronic osteomyelitis.

In brief, when any patient with an infection due to a susceptible organism fails to show a satisfactory response to penicillin, one should review the dosage, search for signs of a bacterial endocarditis, or an abscess which has not been drained.

**Conclusion.** In conclusion, it can be said that penicillin has exceeded our highest hopes as a chemotherapeutic agent. It is unquestionably the most effective agent for the treatment of many infections. There is no other known chemical that is so powerful against bacteria and so harmless to the host.

All of this is most extraordinary when one appreciates that 50 mg. will cure the average gonococcic infection, 300 mg. or less is needed for patients with pneumococcus lobar pneumonia, and 3 to 5 gm. will arrest between 50 and 70% of the infections in subacute bacterial endocarditis.

What we need in the future are effective agents for the similar control of gram-negative bacillary infections and virus infections.

### REFERENCES

1. WARING, A. J., and SMITH, M. H. D.: Combined Penicillin and Sulfonamide Therapy in the Treatment of Pneumococcal Meningitis, *J. Am. Med. Assn.*, **126**, 418, 1944.
2. JOHNSON, L. F., WEINSTEIN, L., and SPENCE, P. S.: Penicillin in Acute Mastoidectomy Wounds With Primary Suture, *Arch. Otol.* (in press).
3. TILLET, W. S., CAMBIER, M. J., and McCORMACK, H. E.: The Treatment of Lobar Pneumonia and Pneumococcal Empyema With Penicillin, *Bull. New York Acad. Med.*, **20**, 142, 1944.
4. MEADS, M., HARRIS, H. W., and FINLAND, M.: Treatment of Pneumococcal Pneumonia With Penicillin, *New England J. Med.* (in press).
5. KIRBY, W. M. M., and HEPP, V. E.: Treatment of Osteomyelitis of the Facial Bones With Penicillin, *J. Am. Med. Assn.*, **125**, 1019, 1944.
6. ANDERSON, D. G., HOWARD, L. G., and RAMMELKAMP, C. H.: Penicillin in the Treatment of Chronic Osteomyelitis, *Arch. Surg.*, **49**, 245, 1944.
7. JEFFREY, J. S., and THOMSON, S.: Gas Gangrene in Italy: A Study of 33 Cases Treated With Penicillin, *Brit. J. Surg.*, **32**, 159, 1944.
8. CUTLER, E. C., and SANDUSKY, W. R.: Treatment of Clostridial Infections with Penicillin, *Brit. J. Surg.*, **32**, 168, 1944.
9. MAHONEY, J. F., ARNOLD, R. C., and HARRIS, A.: Penicillin Treatment of Early Syphilis; A Preliminary Report, *Am. J. Pub. Health*, **33**, 1387, 1943.
10. LENTZ, J. W., INGRAHAM, N. R., JR., BEERMAN, H., and STOKES, J. H.: Penicillin in the Prevention and Treatment of Congenital Syphilis, *J. Am. Med. Assn.*, **126**, 408, 1944.
11. WHITE, W. L., BURNETT, W. E., BAILEY, C. P., ROSEMOND, G. P., NORRIS, C. W., FAVORITE, G. O., SPAULDING, E. H., BONDI, A., and FOWLER, R. H.: Penicillin in Prevention of Postoperative Empyema, *J. Am. Med. Assn.*, **126**, 1016, 1944.

## A STUDY OF THE TYPES OF HYPERSENSITIVITY INDUCED BY PENICILLIN\*

By ADOLPH ROSTENBERG, JR., M.D.

AND

HENRY WELCH, Ph.D.

FOOD AND DRUG ADMINISTRATION  
WASHINGTON, D. C.

FOLLOWING the finding<sup>7</sup> of a case of hypersensitivity of the tuberculin type to crystalline penicillin sodium in an individual who had had no previous contact with this drug, a study was made to determine

\* Presented before the American Public Health Association at the 73rd Annual Meeting in New York, N. Y., October 6, 1944.

the incidence of this type of sensitivity. Studies were made also of the sensitivity induced by the injection of commercial or crystalline penicillin sodium.

To determine the incidence of the tuberculin type of sensitivity to penicillin 144 persons were tested. Each was injected intradermally in the volar surface of the forearm with 0.1 cc. of penicillin sodium containing 1000 units. In all cases where a positive reaction resulted, a retest was made with crystalline penicillin. Of the 144 individuals tested, 106 were healthy inmates of a penal institution, 27 were laboratory personnel, and 11 were employees of manufacturing plants producing penicillin. Eight individuals (5.5%) exhibited hypersensitivity of the tuberculin type when tested initially. Attempts to show a passive transfer of the hypersensitivity using the Prausnitz-Küstner technique and the Urbach-Koenigstein<sup>6</sup> method both failed. (The latter method was attempted with the blister fluid from 5 positives and as many recipients were used.\*)

It had been noted previously<sup>7</sup> that following intradermal injection of commercial penicillin in man there developed a "flaring" phenomenon in certain persons which appeared only after a variable number of injections had been made. This phenomenon consisted of an increase in redness and itching at sites of former injections, following the intradermal injection of crystalline penicillin sodium in a new site. It was also noted that the persons who had exhibited this type of reaction failed to do so after a rest period during which no injections were made. It was decided to study this phenomenon further in view of the fact that these original observations were a by-product of other studies, and consequently the persons manifesting them had not had the same number of injections or the same spacing between injections. Nine individuals were injected intradermally in the volar surface of the lower right arm with 10,000 units of commercial penicillin sodium, 1000 units in 0.05 cc. of saline at each of 10 different sites. These injections were repeated in approximately the same areas 5 days and 10 days later, a total of 30 injections. The material used was commercial penicillin, the products of 7 manufacturers. Following the first series of 10 injections some of the subjects showed evidences of chemical irritation at some of the sites; all who showed the irritation developed it from the same lots of penicillin. Following the second series of 10 intradermal injections reactions occurred in 2 of the people. One individual who had previously received intradermal injections of penicillin showed at the sites of old injections the flaring phenomenon already described. Another developed urticaria approximately 30 hours after injection. The wheals were diffusely distributed, the face and eyelids were swollen, and swelling of the fingers and hands was

\* In order to exclude the possibility that the consistently negative P-K tests were the result of an accidental selection of test subjects incapable of accepting passive transference reagins, serum from a ragweed-sensitive person was also used. At the time the recipients were tested with penicillin they were also tested with a ragweed pollen extract. In all cases positive transference was readily demonstrated with the serum of a ragweed-sensitive person. In the case of the U-K test blisters were raised by means of a cantharides ointment over sites of recently reacting penicillin areas.

pronounced. The individual showed dermatographia, lacrimation and conjunctival injection. The reactions occurred in waves approximately every hour or 2 during the first 4 days but did not stop entirely until 7 days had elapsed. Two days after the reaction had subsided an attempt was made to transfer her sensitivity to 3 normal individuals by the Prausnitz-Küstner technique. Passive transfer was not successful. In view of her general reaction she was tested to determine whether she would exhibit an immediate wheal reaction to the intradermal injection of crystalline penicillin. To avoid a possible systemic reaction, only 50 units of crystalline penicillin sodium were used in the initial test. This was dissolved in 0.02 cc. of saline, injected intradermally in the volar surface of the forearm and the site observed for about 15 minutes. There was no evidence of a reaction. An intradermal test was then made with 200 units of crystalline penicillin in the same manner. A control injection of 0.02 cc. of isotonic saline was made simultaneously. Within 5 to 10 minutes there was a moderate-sized erythematous halo about the site where the crystalline penicillin had been injected and the wheal formed by the introduction of the fluid increased slightly in size. This was considered to be a weakly positive urticarial type of reaction. In contrast to this, the wheal produced by the control injection decreased in size. Another attempt was made, 2 weeks after this this individual recovered, to transfer passively her sensitivity to 4 normal individuals by means of the P-K technique. Again it was found impossible to demonstrate passive transference. Precipitin tests done on 2 occasions on this person's serum were questionable.

For the third series of 10 intradermal injections, 8 persons were used. The reactions following these injections varied considerably. Four of the test subjects showed within 15 to 30 minutes erythema around all injected sites; in some the erythema became confluent (Figs. 1 and 2), and persisted for at least 24 hours. Wheals, varying in size from 5 to 15 mm., developed in 2 of these individuals and then subsided within from 1 to 2 hours. (Fig. 2 shows the wheals well.) The other 4 test subjects showed, in addition to whealing and marked erythema at the sites of injection, the "flaring" reaction at old sites of injection (Fig. 3). One of the latter group of 4 individuals exhibited the most intense reactions. This person received only 4 injections in the third series instead of 10 because he had exhibited a strong flaring reaction following the second series of injections. Within 15 minutes after the third series of injections he showed marked erythema and slight wheals which persisted for only from 1 to 2 hours. Eighteen hours later, at the site of the last 4 injections, erythematous areas redeveloped approximately 30 mm. in diameter and there was marked flaring at all previous sites of injection (Fig. 4). At approximately the 24th hour the 4 sites injected in the third series showed red areas about 25 mm. in diameter surrounded by a narrow, white, non-erythematous zone outside of which was a 3 mm. zone of erythema concentric with the inner one (Fig. 5). The old sites of injection were still flaring at the 30th hour.



FIG. 1

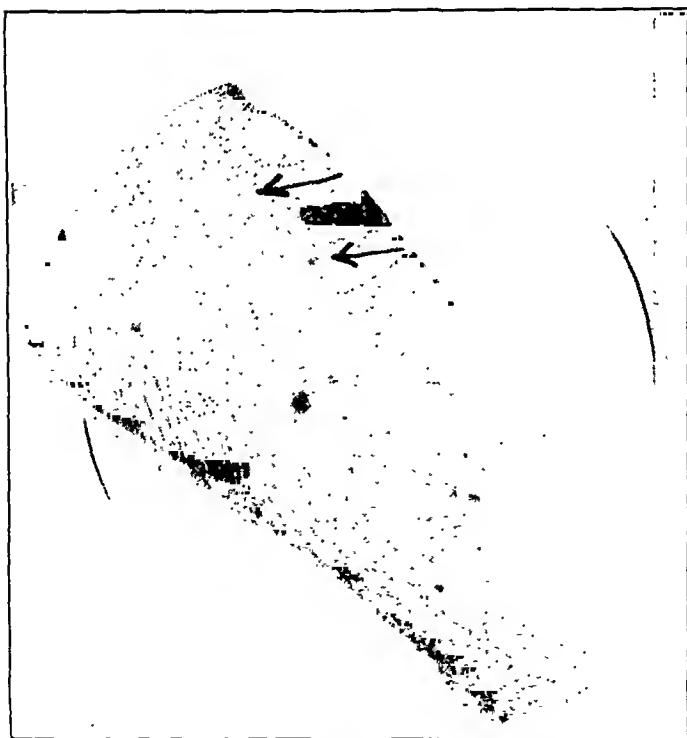


FIG. 2

FIGS. 1 AND 2.—Development of diffuse erythema and wheals following intradermal injection of penicillin sodium.



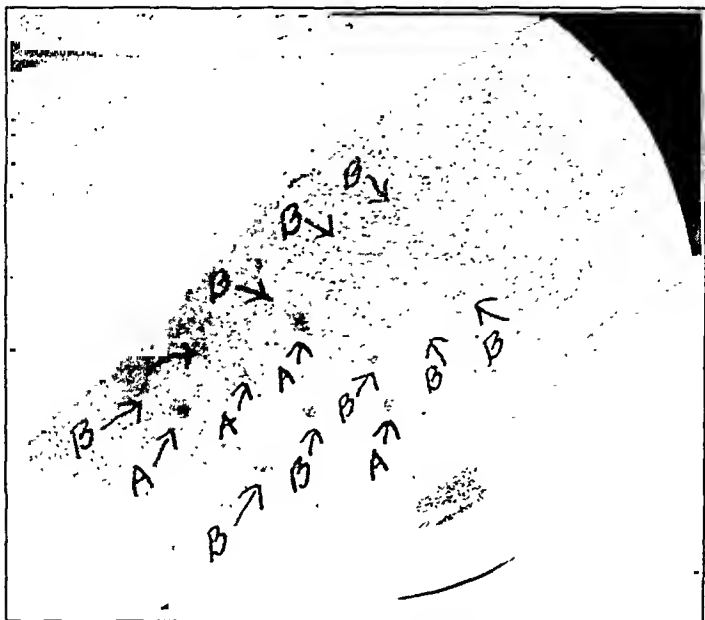


FIG. 3.—“Flaring” of old sites (A) following injection of new sites (B).



FIG. 4.—Marked erythema and “flaring” reaction at old sites 18 hours after intradermal injection of penicillin sodium at four sites marked “A”.

It was decided to attempt to induce sensitivity by varying the technique of administration. Three routes of injection were used. In the first group 10 individuals were given 30 intradermal injections of 1000 units each of commercial penicillin sodium, and 3 individuals were given a similar number of injections of crystalline material, in exactly the same manner as those recorded above, except that the time elapsing between each series of 10 injections was 48 hours instead of 5 days. A second group of 10 individuals was injected subcutaneously, each with 30,000 units of penicillin sodium given in 3 doses of 10,000 units each, 48 hours apart. Finally, a third group of 10 individuals was

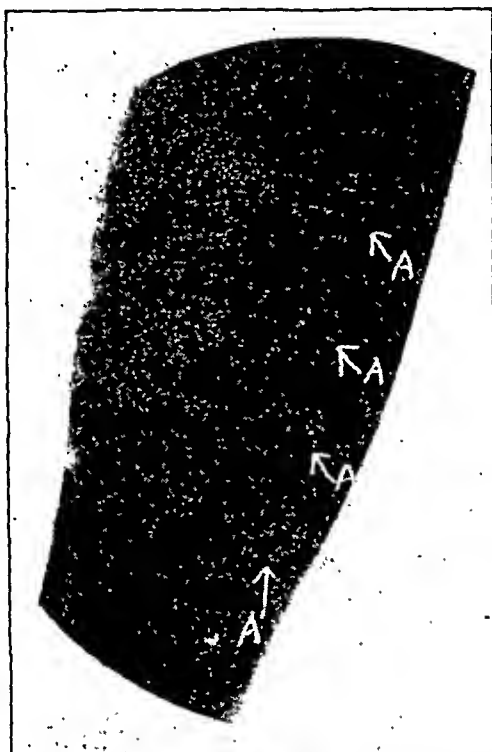


FIG. 5.—Tuberculin type reactions with zones of desensitization (sites marked "A") 24 hours after intradermal injection of penicillin sodium.

injected every 48 hours with 10,000 units of penicillin sodium (5000 units intravenously and 5000 units subcutaneously) until 30,000 units per person had been given.

Only 1 person developed an increase in sensitivity, and this individual was one of those injected intradermally with crystalline penicillin sodium. This person, 24 hours after the third series of injections, showed small-sized tuberculin type reactions at the sites of the injections. Intradermal tests were done with crystalline penicillin on all persons in all groups 48 hours and 1 week after the last injection. All of these tests were negative.

Two individuals not included in the above series had previously shown flaring following the intradermal injection of small amounts of

commercial penicillin sodium. In order to determine whether these persons would still exhibit this phenomenon they were injected in the volar surface of the forearm with 1000 units of crystalline penicillin sodium in 0.05 cc. of saline. No flaring occurred in either individual. It appeared, therefore, that their previous exhibition of flaring was a transient phenomenon. In an effort to reestablish the flaring phenomenon both were given 10 intradermal injections in the volar surface of the forearm, each consisting of 1000 units contained in 0.05 cc. of saline. Within 15 minutes 1 showed moderate erythema and whealing at the sites of injection which persisted for 30 minutes. There was flaring of some but not all of the old sites on the same arm, and this subsided within 2 hours. The other showed a marked erythema in 15 minutes with slight wheals at the sites of the intradermal injections, and in contrast developed, by the 18th hour, marked reddening and swelling at the sites of all injections with some induration which persisted for at least 96 hours after injection. In both individuals the original erythema and the whealing reactions subsided within 2 hours.

Because of the reactions shown, a series of patch tests was made to determine whether the eczematous type of hypersensitivity could be demonstrated. Similar patch tests were made also on 5 of the persons who had shown a tuberculin type of hypersensitivity to crystalline penicillin sodium on initial injection. The tests were made with commercial penicillin sodium, crystalline penicillin sodium, and corn steep liquor, using both normal skin areas and areas which had exhibited previously a tuberculin type of reaction following intradermal injection of penicillin sodium. Although all patch tests were negative, intradermal tests made at the same time with crystalline penicillin sodium again yielded a positive tuberculin type of reaction. From these results it is obvious that none of these test subjects exhibit the eczematous type of sensitivity to either crystalline or commercial penicillin. In this respect these people differ in their hypersensitive state from the individual previously described<sup>7</sup> who showed a tuberculin type of sensitivity to crystalline penicillin sodium and also gave a positive patch test at the site of a previous intradermal injection of either commercial or crystalline material. In order to make sure that the negative reactions were not the result of failure of the material to penetrate the horny layer and thereby reach the shock tissue, areas of the skin of 5 people who had shown a positive reaction following intradermal injection were sand-papered sufficiently to cause an occasional faint pin-point punctum of blood. Patch tests were then made on these sites. These tests were also negative, indicating that the negative patch tests resulted from the lack of a hypersensitive shock tissue rather than from inability of penicillin to penetrate the horny layer.

As stated previously, it was not possible to demonstrate passive transference of the sensitivity exhibited by persons who show a tuberculin type reaction on first contact with penicillin. An attempt was made, therefore, to transfer passively the hypersensitivity exhibited by individuals in whom the hypersensitive state had been induced by

intradermal injection. Four test subjects who had exhibited varying degrees of sensitivity were used and the P-K technique was followed. Passive transfer was attempted to 6 normal persons. Passive transfer antibodies (P-K reagins) could not be demonstrated. Precipitin tests made on the serum of the 4 test subjects were also negative.

One individual who had been a recipient for the passive transfer experiments, although showing no reaction directly after the attempted transfer, exhibited, beginning about 7 days later, a tuberculin type of reaction. This individual reported that on the 6th day following injection the injected areas had itched considerably. On examination on the 7th day his right arm presented 3 erythematous infiltrated areas corresponding to the sites where the penicillin had been injected 7 days previously. The sites where penicillin plus serum had been injected were slightly more inflamed and elevated than the site where the penicillin alone had been injected. The left arm which had received control injections of serum, saline and ragweed showed no reaction whatsoever. This person apparently developed a sensitivity of the tuberculin type as a result of 3 simultaneous intradermal injections of crystalline penicillin sodium of 1000 units each.

To determine whether the sensitivity to penicillin would also extend to the spores of *Penicillium notatum*, a heat-killed suspension was made containing 500,000 spores per cc. Intradermal injections of 0.1 cc. were given to 5 persons who exhibited a tuberculin type of hypersensitivity to penicillin. There were no immediate or delayed reactions. This is in accord with the studies of Feinberg<sup>2</sup> who noted that people sensitive to *Penicillium* sp. did not react to penicillin. We also tested the same 5 persons and several normal controls with various fungous extracts, namely, Trichophyton, Oidiomycin, Haplosporangin, Histoplasmin, Coccidioidin and Blastomycin. There were no significant differences between the penicillin-positive people and the normal controls in their reactions to these extracts.

**Discussion.** It would appear from the results of this investigation that a small, but substantial, percentage of the population is sensitive to crystalline penicillin sodium despite the fact that these individuals have had no contact with this material previously. Since the material at the test strength is not a primary irritant, a positive reaction indicates that these individuals are specifically hypersensitive to this material, and unless a radically new mechanism for such reactions is hypothesized, it must be assumed that these individuals have had previous contact with penicillin sodium or with an immunologically equivalent material. Contact with penicillin sodium as such can be arbitrarily eliminated. However, contact with *Penicillium* sp. appears to be quite likely since it is a fairly common genus of fungi. It may be postulated that this organism is not infrequently ingested or inhaled, producing in susceptible individuals a subclinical infection with a consequent alteration in their immunologic responses.

It is of interest that in the series reported by Lyons<sup>5</sup> and by Keefer<sup>4</sup> an average of about 4% of the individuals treated with penicillin

sodium exhibited an urticarial type of reaction, while in our series about 5% exhibited a tuberculin type of hypersensitivity following intradermal injections of this material. Only 2 hypersensitive persons in our investigations had therapeutic-sized amounts of penicillin. One of these received on one occasion about 10,000 units intravenously and on another occasion about 50,000 units intramuscularly. On neither occasion was there a systemic reaction despite the fact that this individual gave a strongly positive tuberculin type reaction to crystalline penicillin sodium. The other individual exhibited, beginning about 6 to 8 hours after receiving 50,000 units intramuscularly, a diffuse miliary papulovesicular dysidrosiform eruption which persisted for several days. His reaction was apparently identical to that described by Graves *et al.*<sup>3</sup> as were also his immunologic responses to penicillin.

It will be noticed that there was a rather striking disparity in the incidence of reactions produced by the intradermal injection of penicillin depending on the time between successive administrations and the route of administration. Where the intervals between repetitions were 5 days, a relatively high percentage of reactions was obtained in contrast to practically no reactions when the intervals were only 48 hours apart. Furthermore, reactors were obtained only when the penicillin was given intradermally. While it is realized that this series is much too small to have these differences assume any statistical validity and that other variables (such as sex and race) also differed in the series, the impression is gained that frequent injections of penicillin subcutaneously, intravenously, or intramuscularly are less likely to yield adverse reactions than similar injections made intradermally.

The reactions obtained following intradermal injection of penicillin sodium fall into two categories. In the case of the spontaneously sensitive individuals all reactions were of the tuberculin type. In this group there does not seem to be any eczematous or wheal (urticarial) component. In the individuals originally negative but who became hypersensitive following repeated intradermal injections of penicillin sodium the reactions, although eventually developing into a tuberculin type of hypersensitivity, may show transient reactions wheal-like in nature before this stage is reached. These transient reactions appear to be predicated on capillary damage or injury, and simulate in some respects the type of reaction seen in the Arthus phenomenon. The latter reaction, of course, is ordinarily brought about by repeated subcutaneous injections of a soluble protein, while in the case of penicillin sodium the injections were intradermal and the material non-protein. Furthermore, when subcutaneous injections of penicillin sodium were made no reactions were obtained. A possible explanation for the similarity of the reactions obtained with penicillin sodium and those seen in the Arthus phenomenon is that when penicillin is injected subcutaneously or intramuscularly it is excreted very rapidly from the system. Furthermore, from other studies in this laboratory, it is obvious that the penicillin molecule has a strong avidity for protein since it readily conjugates with such substances. It is well known that

substances injected intradermally are excreted much more slowly than when injected by other routes of administration, and consequently it may be possible that penicillin sodium injected intradermally remains *in situ* for a sufficient period of time to combine with body proteins, thus forming a heterologous antigen in which the penicillin molecule acts as a hapten. When penicillin sodium is injected subcutaneously, rapid excretion does not permit sufficient time for the formation of such an antigen. It is possible also that penicillin sodium *per se* can act as an antigen. In this event the reason for the reactions obtained when it is given intradermally and lack of reaction when given subcutaneously may again be because of the time element. The fact that we failed to demonstrate precipitins in the individuals showing the reactions described, militates against the explanation that such reactions were of the nature of the Arthus phenomenon. Failure to demonstrate precipitins, however, may be explained on the basis that the antigen dilution method was used to determine the precipitin titer and this technique, as has been pointed out by Cannon and Marshall,<sup>1</sup> is not suitable for use with sera having low precipitin titers.\* It may be that the reactions observed can be considered as the first stages of an Arthus phenomenon and that continued injection might have developed the more serious necrotic phenomenon and simultaneous development of high precipitin titers. Continued injection in the volunteer laboratory personnel, however, did not appear to be justified.

**Summary and Conclusions.** 1. Five % of 144 individuals tested with crystalline penicillin sodium exhibited a positive reaction of the tuberculin type, despite the fact that none of these individuals had had any prior contact with penicillin.

2. Repeated multiple intradermal injections of penicillin sodium cause the development in some people of reactions of the Arthus type, and some of these also developed a tuberculin type of hypersensitivity.

#### REFERENCES

1. CANNON, P. R., and MARSHALL, C. E.: Studies on the Mechanism of the Arthus Phenomenon, *J. Immunol.*, 40, 127, 1941.
2. FEINBERG, S. M.: Penicillin Allergy, *J. Allergy*, 15, 271, 1944.
3. GRAVES, COM. W. N., CARPENTER, LT. COM. C. C., and UNANGST, LT. (j.g.) R. W.: Recurrent Vesicular Eruptions Appearing During Administration of Penicillin, *Arch. Dermat. and Syph.*, 50, 6, 1944.
4. KEEFER, C. S., BLAKE, F. G., MARSHALL, E. K., JR., LOCKWOOD, J. S., and WOOD, W. B., JR.: Penicillin in the Treatment of Infections: A Report of 500 Cases, *J. Am. Med. Assn.*, 122, 1217, 1943.
5. LYONS, C.: Penicillin Therapy of Surgical Infections in the U. S. Army, *J. Am. Med. Assn.*, 123, 1007, 1943.
6. URBACH, E., and GOTTLIEB, P. M.: *Allergy*, Grune & Stratton, p. 179, 1943.
7. WELCH, H., and ROSTENBERG, A., JR.: A Case of Hypersensitivity of the Tuberculin Type to Crystalline Penicillin Sodium, *J. Am. Med. Assn.*, 126, 10, 1944.

\* If, as suggested above, penicillin acts as a hapten, visible precipitation would not be expected to occur. However, precipitin tests on some of the test subjects repeated approximately 1½ months later with a conjugate of human plasma and crystalline penicillin were negative.

## EFFECT OF SODIUM SALICYLATE ON THE SEDIMENTATION RATE OF ERYTHROCYTES IN VITRO\*

By F. HOMBURGER, M.D.

RESEARCH FELLOW, THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL  
BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services  
[Harvard], Boston City Hospital, and the Department of Medicine,  
Harvard Medical School)

INTEREST in the salicylates has been renewed by Coburn's<sup>2</sup> work on the treatment of rheumatic fever with high doses of salicylates employing blood salicylate levels and determinations of the sedimentation rate as guides for therapy. Many clinicians use the sedimentation rate to judge the effectiveness of therapy in patients receiving salicylates. It is of interest therefore to examine the effect of salicylates on the sedimentation rate of erythrocytes *in vitro*.

In 1932, Bendien, Neuberg and Snapper<sup>1</sup> reported marked slowing of the sedimentation rate following the addition *in vitro* to the blood of at least 100 mg. per 100 cc. of sodium salicylate. In 1941, Lichty and Hooker<sup>6</sup> confirmed these findings and stated that the lowest concentration of salicylate necessary to cause slowing of the sedimentation rate was 90 to 120 mg. per 100 cc. which was at least 3 times the value given by Hanzlik<sup>5</sup> as an average blood level obtainable in rheumatic patients. Bendien, Neuberg and Snapper<sup>1</sup> attributed the action of the salicylates to an increased stability of the colloidal state of the plasma proteins. The plasma fibrinogen concentration, plasma viscosity and the red blood corpuscles were unaltered. This view is supported by the more recent experiments of Coburn,<sup>3</sup> showing that the addition of sodium salicylate to rabbit serum modifies the precipitation of serum proteins by sodium tungstate and also partially inhibits the precipitation of horse serum euglobulins by rabbit antiserum.

In the present experiments the *in vitro* effects of salicylates in concentrations comparable to therapeutic levels were investigated.

**Methods.** The following methods were used in all experiments unless modifications are noted specifically.

1. The *corrected sedimentation rate* (C.S.R.) was determined by the method of Rourke and Ernstene,<sup>8</sup> using as anticoagulant a dry mixture of 4 mg. of potassium oxalate and 6 mg. of ammonium oxalate for each 5 ml. of blood.

For the study of the effects of salicylate, the plasma was separated from the cells by slow spinning and transferred into test tubes in amounts of 2 ml. per tube; the sodium salicylate was then added in the form of a solution of 2 gm. in 100 ml. of isotonic sodium chloride solution. One tube was left without salicylate, as a control; to the others were added amounts to make concentrations of 12, 30, 60, 90, 120, 150, 180 and 210 mg. of sodium salicylate per 100 ml. of plasma. The quantities of diluent were kept the same in all tubes by the addition of physiologic saline solution in amounts inversely proportional to the quantities of sodium salicylate solution used. Plasma thus prepared was kept sterile and was left standing for various lengths of time. In order to determine the C.S.R. in such plasmas, fresh cells were obtained from

\* This study was aided in part by a grant from the Ella Sachs Plotz Foundation, in recognition of Dr. Francis W. Peabody's services to the Foundation.

the same individual by slowly centrifuging oxalated blood and pipetting the cells into the prepared plasmas in amounts resulting in the original hematocrit value. Plasma and cells were left in contact for 30 to 120 minutes and the C.S.R. was then determined as usual. All results are given in millimeters per minute and are corrected for a hematocrit of 45%, according to the chart of Rourke and Ernstone.<sup>8</sup> The use of this chart in the presence of salicylate is justified because this salt does not alter the mean corpuscular volume and because the relation between C.S.R. and hematocrit was found to be unchanged by the addition of salicylate.

2. Different *plasma fibrinogen* levels were obtained in normal plasma by the addition of human plasma fibrinogen purified by electrophoresis.\* The plasma fibrinogen determinations were done by the Cullen-Van Slyke method in citrated plasma.<sup>4</sup>

3. *Salicylate levels* in plasma and serum were measured by the method used by Coburn.<sup>2</sup>

4. The Beckman pH meter equipped with glass electrode served for the determination of the H ion concentration in the plasma.

**Experiments.** 1. THE EFFECT OF SODIUM SALICYLATE ON THE C.S.R. OF NORMAL BLOOD ADJUSTED TO DIFFERENT PLASMA FIBRINOGEN LEVELS. By addition of human plasma fibrinogen to normal plasma, fibrinogen levels of 662, 467, 318 and 242 mg. per ml. were obtained. Each fraction of plasma was divided into 8 sub-fractions to which varying amounts of sodium salicylate were added. The plasma samples thus obtained contained 0, 30, 60, 90, 120, 150, 180 and 210 mg. of sodium salicylate per 100 cc. of plasma. One-half of each sample was left standing for 30 minutes. Fresh cells were then added and the C.S.R. determined after another 30 minutes. To the remaining half of each sample fresh cells were added after plasma and salicylate had been left in contact for 24 hours at room temperature and the C.S.R. was determined 30 minutes later. A few samples were treated in the same manner except that the plasma and salicylate were left in contact for 24 hours in a water bath at 37° C. *Results:* (Chart 1, left side, and Chart 2.) In the plasma which had stood for 30 minutes in contact with salicylate marked slowing of the C.S.R. was observed at drug levels of 90 mg. per 100 ml. or higher. When the contact of plasma and salicylate extended over 24 hours at room temperature this effect was more marked and occurred at levels as low as 30 mg. per 100 ml. The C.S.R. was not significantly altered in the salicylate-free controls. When plasma was incubated for 24 hours at 37° C. even the controls were significantly slowed and consequently the C.S.R. in samples containing salicylate was no longer readable.

2. EFFECT OF SODIUM SALICYLATE ON THE C.S.R. OF BLOOD FROM PATIENTS WITH VARIOUS DISEASES. (Chart 1, right side.) Blood with accelerated C.S.R. was taken from patients with various diseases, and the plasma left in contact with sodium salicylate for 24 hours at room temperature. Fresh cells of the same individuals were then added and the C.S.R. determined. *Results:* A marked reduction of the C.S.R. followed the addition of sodium salicylate in all these cases and amounts comparable to therapeutic levels reduced the C.S.R. to normal values.

\* The fibrinogen used was a sample prepared by the Harvard Plasma Fractionation Laboratory and obtained through the courtesy of Prof. E. J. Cohn.



3. POSSIBLE MECHANISMS OF EFFECT. (a) Numerous *plasma fibrinogen* concentrations were determined in plasmas containing varying amounts of sodium salicylate. Even in samples showing extreme retardation of the C.S.R. the plasma fibrinogen levels were not significantly altered.

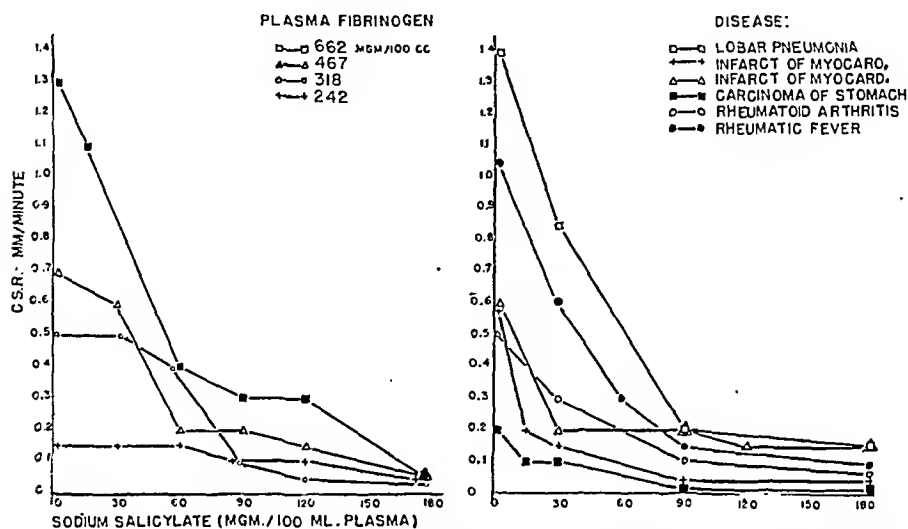


CHART 1.—Slowing of sedimentation rate by sodium salicylate *in vitro* in blood from various patients (right) and in normal blood adjusted to different fibrinogen levels by addition of purified fibrinogen (left).

PLASMA-SALICYLATE CONTACT 2 HOURS

PLASMA-SALICYLATE CONTACT 24 HOURS

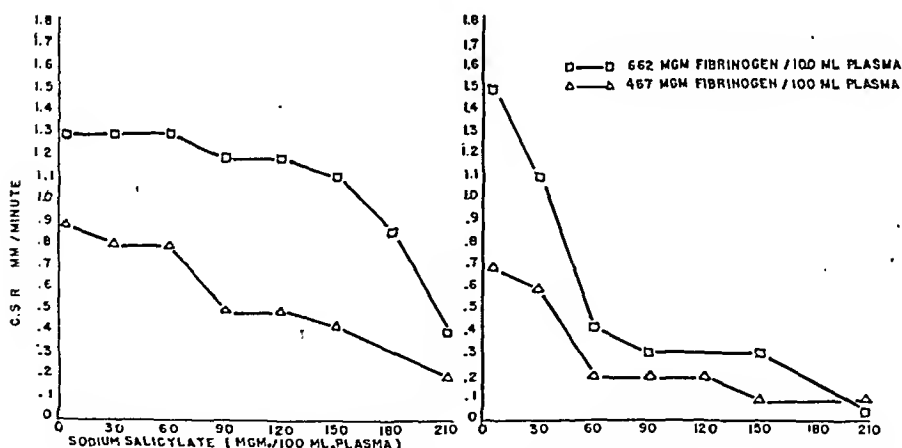


CHART 2.—Slowing of sedimentation rate by sodium salicylate *in vitro* in blood adjusted to different fibrinogen levels.

(b) *Red blood corpuscles* were suspended in normal plasma after having been exposed to mixtures of plasma and salicylate which had been standing at room temperature for 24 hours. In all cases, even after remaining in contact with such mixtures for 2 hours, the C.S.R. of these erythrocytes in normal plasma was the same as before exposure to salicylates.

(c) The effect of other sodium salts (Chart 3) was tested by replacing the sodium salicylate by equal amounts of sodium benzoate and sodium bicarbonate. Neither of those salts had any effect nor did sodium bicarbonate inhibit the action of the sodium salicylate.

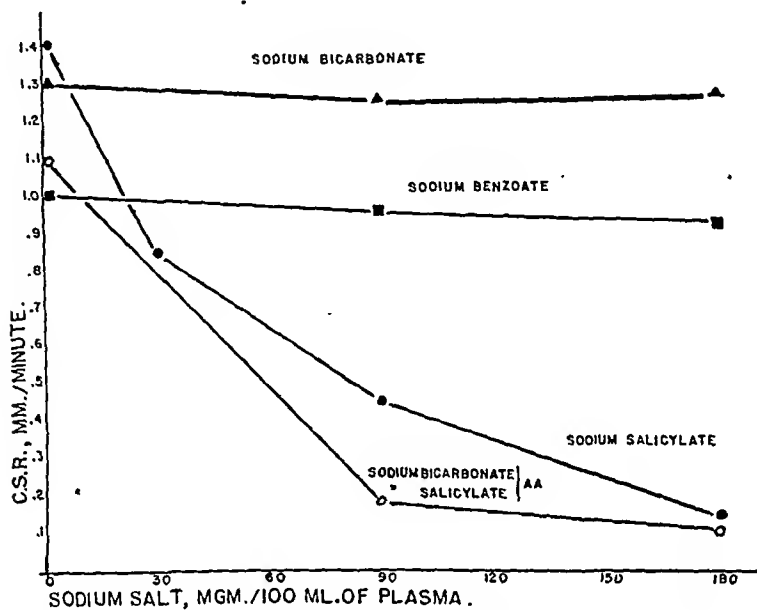


CHART 3.—Effects of sodium salts upon sedimentation rate *in vitro*.

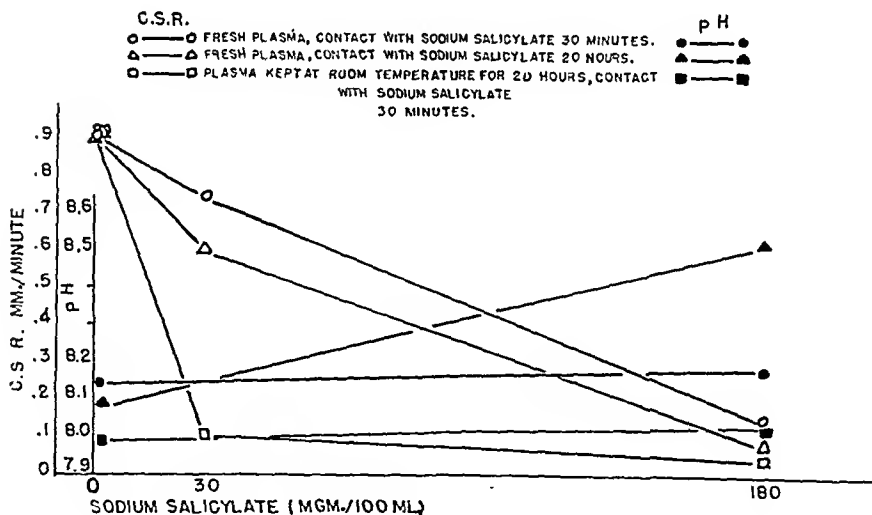


CHART 4.— $H^+$  ion concentration in plasma in relation to sodium salicylate effect.

(d) If the *salicylate radical* became *conjugated with fibrinogen* (Table 1) it would be likely that part of the salicyl radical would no longer be contained in the serum after coagulation of the fibrinogen by recalcification and that the plasma might lose free salicyl radical through prolonged contact with it as the method used for its determination is specific for *free salicyl*. The experiment tabulated in Table 1 demon-

strates that this does not take place. Some salicyl radical is lost to the erythrocytes after 24 hours as described earlier by Bendien, Neuberg and Snapper.<sup>1</sup>

TABLE 1.—THE FATE OF SODIUM SALICYLATE IN FULL BLOOD, PLASMA AND SERUM AFTER STANDING AT ROOM TEMPERATURE FOR 24 HOURS

No.	Description of sample examined	Salicylate (mg. per 100 ml.)	
		After 2 hrs.	After 24 hrs.
1	Salicylate solution and saline (5 ml. of each)	114	117
2	5 ml. of salicylate solution, 4.5 ml. saline, 0.5 ml. of 2.5% sodium citrate	110	112
3	5 ml. of salicylate solution, 4.5 ml. of serum, 0.5 ml. of 2.5% sodium citrate	97	93
4	5 ml. of salicylate solution, 4.5 ml. of plasma, 0.5 ml. of 2.5% sodium citrate	96	109
5	Same as No. 4 after recalcification and centrifuging off the fibrin clot	96	108
6	Same as No. 4 with cells added, left in contact for 24 hours, then centrifuged off	..	70

NOTE.—The technical error of the method in our hands is approximately + or - 15%.

(e) *Changes in the pH of the plasma* (Chart 4) during standing at room temperature and after addition of sodium salicylate were investigated. According to Nichols<sup>7</sup> there is a difference of opinion as to whether variations in pH influence sedimentation rate. In the present experiments there were measurable changes in H<sup>+</sup> ion concentration but there was no causal relationship between these changes and those of the C.S.R.

(f) *Standing at room temperature* may be an important factor. Not only is the salicylate action increased, but mere standing of the plasma alone for 20 hours at room temperature considerably increases the effect of sodium salicylate when this is added thereafter and the C.S.R. determined within 30 minutes after addition of the salt.

**Discussion.** Thus, sodium salicylate, *in vitro*, has the effect of slowing the sedimentation rate by a mechanism as yet unexplained, but probably related to changes in the stability of the colloidal state of the plasma.<sup>1,3</sup> This effect takes place immediately following the addition of sodium salicylate in concentrations considerably larger than those reached *in vivo*, as previously shown by Bendien, Neuberg and Snapper<sup>1</sup> and by Lichty and Hooker.<sup>6</sup> When the contact between sodium salicylate and plasma is prolonged for 20 hours at room temperature under sterile conditions, salicylate levels as small as those seen in patients under salicylate therapy cause marked slowing of the C.S.R. Leaving pure plasma at room temperature, before salicylate is added, results in a markedly enhanced effect of the latter. This effect of salicylate is non-specific and occurs in blood artificially enriched in fibrinogen as well as in blood of patients with various diseases.

**Conclusion.** It seems possible that this property of sodium salicylate, demonstrable *in vitro*, may partly account for the remarkable slowing of the sedimentation rate seen in some patients who receive salicylates. This problem deserves further investigation.

**Summary.** 1. Sodium salicylate *in vitro* causes a marked reduction of the sedimentation rate of erythrocytes, particularly if it is accelerated.

2. In fresh plasma this effect takes place at salicylate levels of about 90 mg. per 100 ml.

In plasma which has been kept at room temperature for 24 hours the effect takes place at levels of 25 to 30 mg. of salicylate per 100 ml. of plasma.

When salicylate is left in contact with fresh plasma for the same length of time, the slowing of the sedimentation rate occurs at low levels. The standing of plasma at room temperature has an insignificant effect on the sedimentation rate of fresh red blood corpuscles in such plasma.

No demonstrable changes of plasma fibrinogen or red cells are caused by sodium salicylate and changes of the pH in the plasma do not account for the effect of sodium salicylate on the sedimentation rate. The effect is inherent in the salicylate radical, as sodium benzoate and sodium bicarbonate are ineffective.

#### REFERENCES

1. BENDIEN, W. M., NEUBERG, J., and SNAPPER, I.: *Biochem. Ztschr.*, **247**, 306, 1932.
2. COBURN, A. F.: *Bull. Johns Hopkins Hosp.*, **73**, 435, 1943.
3. COBURN, A. F., and KAPP, E. M.: *J. Exp. Med.*, **77**, 173, 1943.
4. CULLEN, G. E., and VAN SLYKE, D. D.: Quoted by Peters, J. P., and Van Slyke, D. D., *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins, vol. 2, p. 696, 1932.
5. HANZLIK, P. J.: *Medicine*, **5**, 197, 1926.
6. LICHTY, J. A., JR., and HOOKER, S. P.: *Proc. Soc. Exp. Biol. and Med.*, **48**, 69, 1941.
7. NICHOLS, R. E.: *J. Lab. and Clin. Med.*, **27**, 1317, 1942.
8. ROURKE, M. D., and ERNSTEN, A. C.: *J. Clin. Invest.*, **8**, 545, 1930.

### THE ERYTHROCYTE SEDIMENTATION RATE IN RHEUMATIC FEVER

#### ITS SIGNIFICANCE IN ADOLESCENT AND OVERWEIGHT CHILDREN

BY T. N. HARRIS, M.D.

DIRECTOR OF THE RESEARCH LABORATORY, THE CHILDREN'S SEASHORE HOUSE FOR  
INVALID CHILDREN, ATLANTIC CITY, N. J.

(From the Children's Seashore House for Invalid Children, and the Department of  
Pediatrics, School of Medicine, University of Pennsylvania)

AN important problem which arises in the management of rheumatic fever is that of the length of the period of bed rest following the acute stage. Too short a period of bed rest may cause additional damage to the heart, whereas an unnecessarily long period is undesirable for economic and psychologic reasons. In the absence of a specific test for the state of activity of the rheumatic process, non-specific ones are employed. The criteria in use include normal temperature and pulse rate, white and red blood corpuscle counts and erythrocyte sedimentation rate (ESR). All of these serve also as criteria of absence of infection or inflammation of any kind in the body.

Of these tests, the sedimentation rate is in the great majority of cases the most sensitive. After physical findings have become stabilized, the symptoms of active rheumatic infection have disappeared,

and the temperature, pulse rate, respiratory rate and blood counts have returned to normal limits, the rate of erythrocyte sedimentation often remains higher than the accepted normal values, and higher than is normal for the patient. Accordingly, the ESR has become accepted as the finest criterion of complete clinical quiescence of the rheumatic process, and convalescents from rheumatic carditis are maintained in complete bed rest until the sedimentation rate finally reaches the accepted normal limits.

The application of the erythrocyte sedimentation test in this way depends upon the assumption that there is at the time no other process in the body which of itself increases the sedimentation rate. As the test is generally understood, this means that one assumes there exists no other major area of inflammation, in its broad sense of infection, tissue destruction or tissue absorption. This assumption is usually taken to be satisfied if the rheumatic patient shows no evidence of acute infection at the time of the test and has had no acute infection within 2 or 3 weeks. In a patient otherwise apparently well, the failure of the result of the sedimentation test to return to accepted normal values is regarded as evidence of continuing activity of the rheumatic process.

In the course of the past few years the author has, however, observed a few children convalescing from acute rheumatic carditis in whom the ESR did not return to normal limits for very considerable periods of time after all other indications of rheumatic activity had passed. These children were almost all girls, in the adolescent or pre-adolescent age group. About half of these patients were overweight. Finally, when the suspicion became strong that in these particular children the erythrocyte sedimentation test was not a measure of the degree of rheumatic activity, they were gradually allowed increasing physical activity up to the limit of normal activity of the quiescent rheumatic patient.

Since it was, in effect, being assumed that the rheumatic process was quiescent, despite the elevated ESR, it was particularly important to determine whether this treatment was justified by the subsequent clinical course, after the resumption of physical activity. Accordingly, careful clinical observations were continued during this period.

**Clinical Material.** The 9 children whose histories will be summarized were under the author's care at the Children's Seashore House for Invalid Children at Atlantic City. Two of them were later followed in Philadelphia at the Cardiac Clinic of the Children's Hospital. They were admitted to the Children's Seashore House from hospitals in Pennsylvania and New Jersey in various stages of convalescence from rheumatic carditis. The ages ranged from 9 to 16 years. They were all girls with the exception of 1 boy who was rather obese. Several of these girls were also overweight. During the 3½ year period during which observations were made, other rheumatic children convalescing from carditis were observed and treated by the author in the same institution in exactly the same way as these 9 patients. The entire group included 400 patients. They were distributed among the ages of 5 to 16 years and rather evenly between the sexes. In all of these children, the return of the ESR toward normal limits could be observed, or, in some quiescent cases, its value was within accepted normal limits when they entered the Children's Seashore House.

**Methods.** During the entire period of observation of each child, both before and after the patient was allowed out of bed, the following examinations were made periodically:

1. Examination of the heart, including the determination of the position of the apex beat, quality of sounds, murmurs and their transmission, thrills and friction rubs, and cardiac rate and rhythm.

2. General physical examination, including a check on signs of circulatory failure, chorea, pharyngitis, rash, subcutaneous nodules and weight loss.

3. Questioning of patients and nurses as to appearance of characteristic symptoms associated with rheumatic activity such as headache, anorexia, nausea, vomiting, pain (in precordium, chest, abdomen or joints), epistaxis, and general lack of well-being.

4. Recording of such episodes as pharyngitis or other respiratory infections.

5. Laboratory examination, including determination of hemoglobin concentration in blood, red and white corpuscle counts and erythrocyte sedimentation rate. These determinations were always made at the same time of day. Bacteriologic cultures of the nasopharynx and throat were also made at regular intervals. The ESR was measured in mm. of free fall per hour, as described below.

**Results.** The period of treatment by bed rest, and the ESR at the end of that time, are shown in Table 1. In 7 of the 9 cases, the patients were kept on bed rest for over 1 year before it was decided to allow them up in spite of an unduly high ESR. In 1 extreme case 2 years elapsed. The ESR at the time these patients were allowed their first activity out of bed ranged from 20 to 36 mm. of free fall per hour. The children were observed for periods averaging 7.3 months, thereafter. In 1 case the ESR fell substantially during this time, and in 2 other cases there was a slight fall in the ESR (of 6 or 7 mm. per hour) after the patient was allowed to resume activity.

TABLE 1.—CASES OF PROLONGED ELEVATION OF THE ESR

Case No.	Age	Sex	Months of bed rest at CSH before allowed up	Cardiac status at that time		ESR at that time (mm. of free fall per hr.)	Corresponding ESR at 45% packed RBC volume*	Length of observation thereafter (mos.)	ESR at time patient last seen
				Position of apex beat (cm. from mid-line)	Cardiac lesion				
40	13	F	18	7.6	None	20	22	3	20
117	12	F	18	7.2	None	26	28	15	14
124	10	F	24	7.0	M.I.	32	32	5	30
136	9	F	16	7.0	None	30	25	20	28
157	16	F	15	11.2	M.I., A.I.†	36	30	3	32
158	15	F	17	10.6	M.I.	32	26	6	30
216	10	F	12	6.8	None	26	22	5	28
222	14	M	11	8.2	M.I.	24	21	5	18
381	13	F	5	9.0	M.I.	30	26	4	23

\* Using the Ordway-Singer nomogram<sup>13</sup> derived from the Rourke-Ernstene chart.<sup>15</sup>

† Mitral insufficiency, aortic insufficiency.

Table 1 shows also that the degree of cardiac damage varies quite widely among the patients described. Of the 5 apical systolic mur-

murs corresponding to the notation of mitral insufficiency, 1 was transmitted to the posterior axillary line, 2 to the mid-axillary line, and 2 were localized to the apex. Some of the results of the periodic examinations of the children are shown in the chart for each patient, for the entire period of observation.

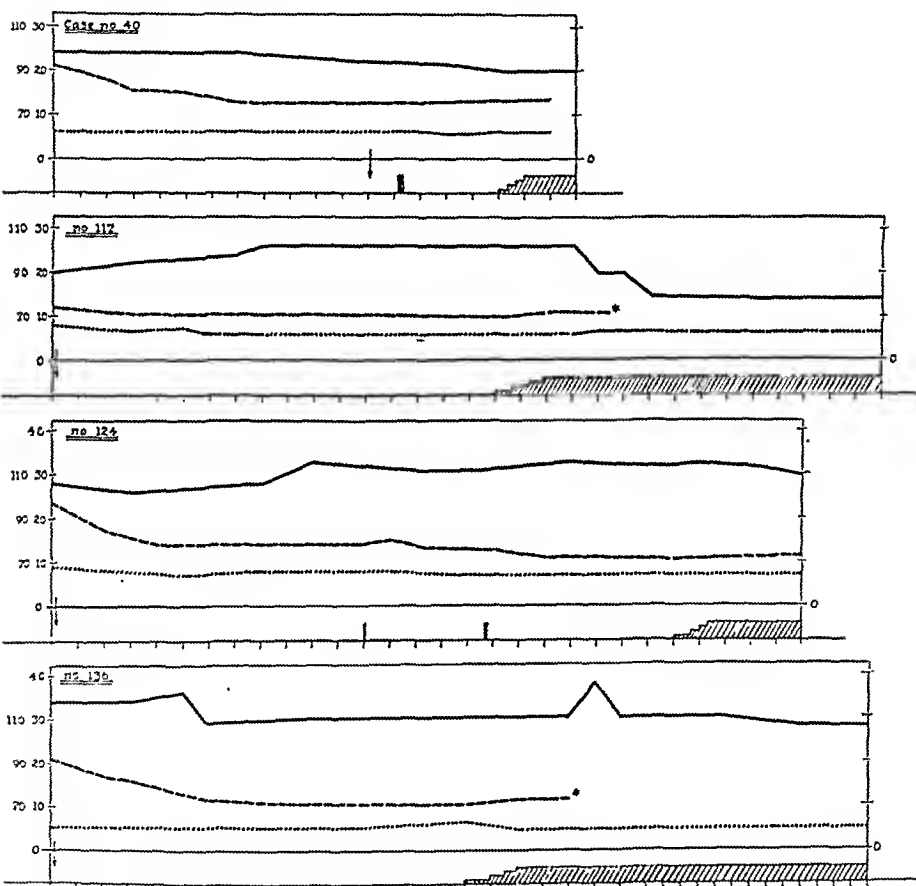
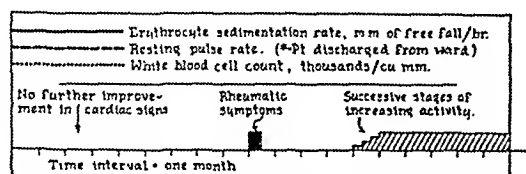


CHART 1.—Effect of increasing activity on ESR, resting pulse rate, and white blood cell count in 4 cases.

1. Examination of the heart: In general, successive examinations showed a tendency of the findings to change in the direction of normal values, until they became constant. The vertical arrow in the charts indicates the time at which the cardiac findings became constant. In some cases, there was no improvement after the admission examination.
2. Symptoms and general physical signs characteristic of rheumatic infections: These, unless clearly attributable to a cause other than the

rheumatic infection, are represented by a vertical line on the base line corresponding in breadth to the duration of the symptoms.

3. Resting pulse rate: These were averaged for each month from weekly rates determined during sleep.

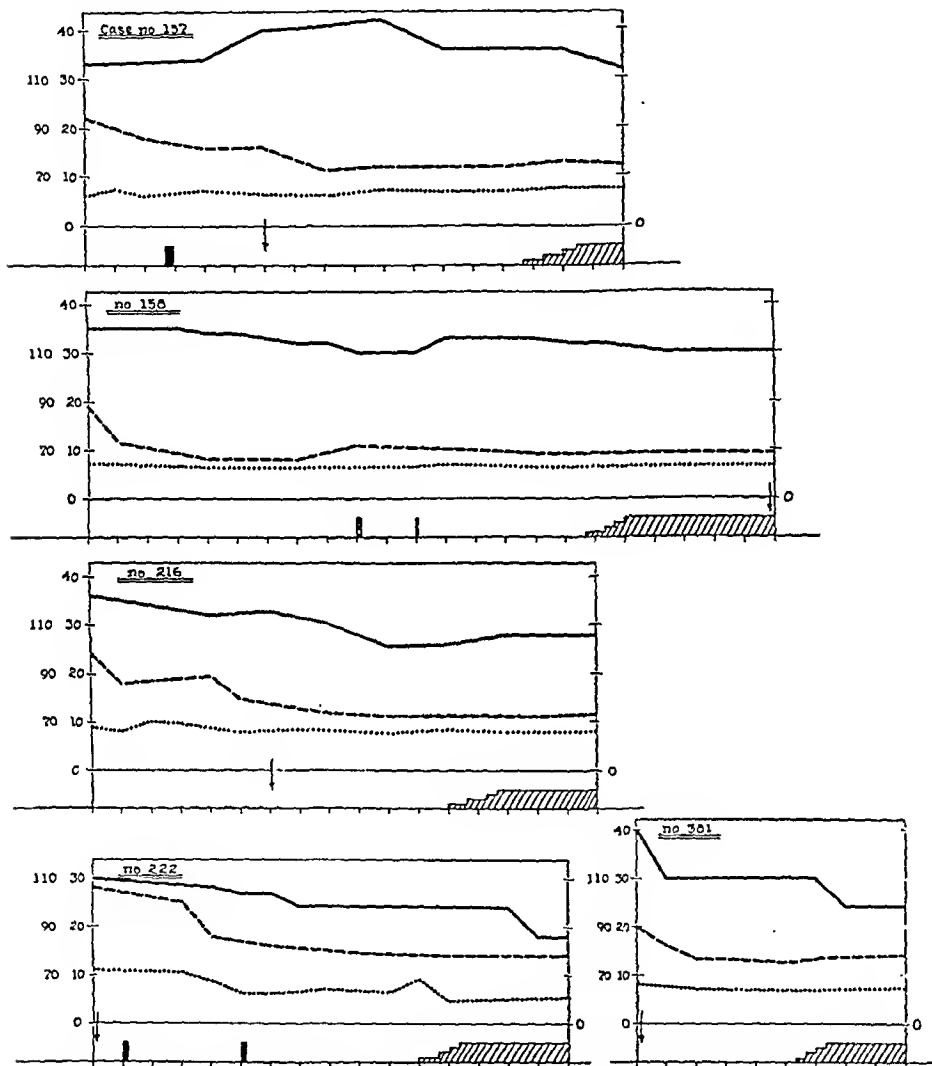


CHART. 2.—Effect of increasing activity on ESR, resting pulse rate, and white blood cell count in 5 cases.

4. Increasing amounts of activity permitted the patient are indicated by the stepwise rise of the line in the lower right corner of each chart: bathroom privileges, then 1, 2 and, finally, 4 hours out of bed. The first 2 hours out of bed were given over to the supervised activity of the classroom and the occupational therapy shop. Markers along the base line indicate months.

It is the purpose of the chart to indicate significant developments in the clinical course of each patient under discussion. In addition to



the signs, symptoms and tests indicated, there was no weight loss, fever, increase in respiratory rate or decrease in hemoglobin value during the period of observation following resumption of physical activity. As will be seen in the charts, in none of these children was there any indication, by any of the tests mentioned, that the patients had been allowed out of bed prematurely.

Control observations were made on 391 other children who completed their convalescence from rheumatic fever at the Children's Seashore House. With the few exceptions indicated below, the ESR fell in the usually observed manner to 15 mm. per hour or below, usually within about 1 month of the cessation of other conventional indications of rheumatic activity. The fall of the ESR from values of over 40 mm. of free fall per hour usually required only a few weeks.

**The Technique Employed by the ESR Test.** The erythrocyte sedimentation rate was determined in mm. of free fall per hour by recording the height of the erythrocyte column at 5 minute intervals for  $\frac{1}{2}$  hour. The time-lag due to the rouleaux formation was eliminated by beginning the readings only after some observable sedimentation had taken place. The error due to packing of red blood corpuscles was obviated by using a 100 mm. tube and by dropping the last reading or two if they fell out of the arithmetic progression. In this way the determination of rate of free fall of rouleaux is based on a number of mutually corroborative observations during successive intervals rather than one or two. The measurement of this physical property of the blood is the basis of all techniques of determining the ESR now in general use.<sup>7,12,15,19,23</sup>

No attempt can be made here to enter into the vexed question of the necessity for and the correct method of routine "correction for anemia."<sup>1,2,4-6,8-11,15-18,20-22</sup> This question is not of decisive importance for the purposes of this paper, since the hemoglobin values and packed red corpuscle volume percentages of the patients described were in no case far from normal. This was probably a consequence of months of good institutional care in the absence of active rheumatic disease. As Table 1 shows, in no case was the difference between the original and adapted ESR greater than 6, and in 2 cases the adjustment to 45% packed red corpuscle volume gave a higher result.

The question of normal limits of the ESR is, again, not within the scope of this paper. During the past 4 years the ESR was determined in this way for 400 patients who convalesced in this institution from rheumatic carditis, and 82 patients with chorea. In addition to the rheumatic group there were patients convalescing from nephritis, upper respiratory infection, malnutrition, and so forth. Almost all of these children reached an ESR of below 15 mm. per hour of free fall or showed such an ESR on admission. The lowest recorded was 3 mm. per hour. The only exceptions to this range in the absence of intercurrent infection were 3 rheumatic patients, 2 of whom were severely anemic because of symptomatic epistaxis, and 5 other rheumatic patients, all girls, who reached levels of between 15 and 18 mm. per hour. These last were not included in this paper because their ESR was so near the normal range for the group.

The values of the ESR shown in Table 1 are, then, definitely out of the range of normal for the group. They would all be considered abnormal according to the authors of four of the five techniques mentioned above, and 6 of the 9 would be considered outside normal limits by the fifth method, the Rourke-Ernstene technique.<sup>15</sup>

**Discussion.** The data presented in this paper have both theoretical and practical implications. The theoretical implications are quite obscure, inasmuch as we understand today neither the basis for increased ESR nor the mechanism of rheumatic infection. The ques-

tion arises: Are these instances of persistent elevation in ESR a result of interrelation of the rheumatic process and a factor present in some adolescent children, or are they merely a result of random sampling in a group of adolescents, in which some instances of elevated ESR are found? The latter alternative, in turn, poses a prior question: Is there, in the distribution of ESR values in adolescents, a number of apparently normal healthy children, especially girls, whose ESR falls outside the general range of normal values?

In the standardization of the various techniques of determining the ESR there has been no emphasis on normal values in the age-sex group under consideration. Two studies have been reported, however, on the range of ESR observed in presumably normal girls in the adolescent and pre-adolescent age group. In one study<sup>14</sup> it was found that although the mean ESR of 87 adolescent subjects was 10 mm. per hour, 5% showed values over 40. In another study,<sup>3</sup> 327 normal girls of adolescent and pre-adolescent age were examined by the Cutler technique. It was found that 8% of the subjects had ESR values ranging from 14 to 25, the others falling within the normal limits found by Cutler in standardizing his method. The question of latent infection as a possible cause of the higher values found in this group was subjected to very careful control, but months of observation thereafter revealed no pathologic cause for the higher values. A greater mass of data would seem to be necessary if this is to be accepted as a part of the natural history of adolescence. If such confirmation is made then, as further data are accumulated on the distribution of values of ESR in healthy and in rheumatic adolescent girls, it may become possible to show whether the elevated ESR values found in the rheumatic groups are simply a result of random sampling of an effect of adolescence, or whether they result from an interaction of phenomena. It should also be of considerable interest to determine the distribution of ESR values in adolescent girls convalescing from other chronic diseases which elevate the ESR, such as tuberculosis and nephritis.

The observations reported here would also seem to have a practical implication for the management of convalescence from acuterheumatic carditis in the case of adolescent patients.

It is unfortunate that in rheumatic fever the more specific parts of the clinical picture, cardiac signs and symptoms, usually return toward normal limits earlier in convalescence than do the non-specific signs. The erythrocyte sedimentation test bears the special responsibility of being used in the great majority of cases as the criterion for beginning the increase in the patient's activity. The observations presented above would seem to affect the interpretation of an elevated ESR in rheumatic fever in adolescent patients, especially girls, when it persists for some time as the only indication of activity of the rheumatic process.

An examination of the clinical chart will show that in such cases a number of months may be spent by the patient in bed while the ESR remains elevated as the only indication of rheumatic activity, and this prolonged stay in bed is not well borne by children who are not actually ill. This is especially true in the older age groups among children, in

which the phenomenon has been observed. Under these circumstances it is, after a time determined by clinical observation, both unnecessary and harmful to continue complete bed rest while waiting for the ESR to return to normal limits.

It need hardly be said that where any doubt exists as to the status of the patient, complete bed rest is advisable and should be continued. Certainly it is far better to err in the direction of too long a period of complete bed rest than to allow the patient increased activity prematurely. Finally, the continued examinations which would invariably be made under the circumstances, as the patient is carefully permitted increasing activity, would serve to confirm the clinical judgment in such cases.

No attempt has been made to estimate the expected frequency of the phenomenon described here because of the small number of cases observed and because of the lack of general agreement as to the normal range of ESR values. For orientation, however, it may be indicated that within this group of 400 convalescent rheumatics, the 9 cases described here represent 2.3% of the total, or 3.6% of the 248 patients who fell in the age range of 9 to 16 years. In the girls' wards the 8 cases represent 3.7% of the 215 patients, or 6% of the 133 girls in the 9 to 16 year range.

The term "rheumatic activity" has been avoided as much as possible because of our present lack of understanding of the nature of the rheumatic process and the consequent subjective factor involved in the use of the term. The children described in this paper have not been identified as "active" or "inactive rheumatics" in the terminology of rheumatic disease. Rather the quiescence of the rheumatic process affecting these children at the time they were allowed up has been indicated in terms of their subsequent tolerance of progressively increasing exercise, as observed data in the clinical charts. This is, in fact, the practical criterion in the management of convalescence from rheumatic carditis when one considers allowing the patient up.

It is of interest to report, in this connection, that of the control patients, 3 children who were allowed out of bed after the subsidence of all signs of rheumatic infection and the fall of the ESR to normal levels, in the usual manner, showed clinical evidence immediately thereafter that they had resumed activity prematurely. These children were returned to bed; their ESR values fell again, and the subsequent clinical course was uneventful.

In considering the possibility that the persistence of the elevated ESR in the patients described might be due to an unrecognized smouldering rheumatic lesion, it is pertinent to point out that the degree of cardiac damage was found to vary quite widely among the group, and that in 4 of the 9 no cardiac lesion was demonstrable during the greater part of their convalescence.

**Summary.** Four hundred children, 215 of whom were girls, were observed during their convalescence from episodes of rheumatic carditis. In 9 of these patients, 8 girls and 1 boy, ranging from 9 to 16 years of age, the ESR remained persistently elevated long after the other signs,

symptoms and tests for active rheumatic infection had returned to normal or become stationary. These patients were ultimately allowed out of bed while the ESR was still elevated. Continued clinical observation following the resumption of physical activity failed to reveal any indication that these children had been allowed out of bed prematurely.

Some theoretical and clinical implications of these data are discussed.

#### REFERENCES

1. BANNICK, E. G., GREGG, R. O., and GUERNSEY, C. M.: J. Am. Med. Assn., 109, 1257, 1937.
2. BELK, W. P., and WILSON, M. K.: Penna. Med. J., 45, 1045, 1942.
3. BENSON, L., and ROGERS, E. J.: J. Lab. and Clin. Med., 26, 987, 1941.
4. BOERNER, F., and FLIPPIN, H. F.: J. Lab. and Clin. Med., 20, 583, 1935.
5. BOUTON, S. M., JR.: J. Lab. and Clin. Med., 23, 519, 1938.
6. CROMBIE, D. W., and HAMBLETON, A.: Canad. Med. Assn. J., 39, 162, 1938.
7. CUTLER, J. W., PARK, F. R., and HERR, B. S.: AM. J. MED. SCI., 195, 734, 1938.
8. CUTLER, J. W.: J. Lab. and Clin. Med., 26, 542, 1940.
9. HAMBLETON, A., and CHRISTIANSON, M. D.: AM. J. MED. SCI., 198, 177, 1939.
10. HUBBARD, R. S., and GEIGER, H. B.: J. Lab. and Clin. Med., 13, 322, 1928.
11. LEBEL, H., and LOTTRUP, M. C.: Acta med. Scandinav., 80, 550, 1933.
12. LINZENMEIER, G.: Arch. f. d. ges. Physiol., 181, 169, 1920.
13. ORDWAY, N. K., and SINGER, R. B.: In preparation.
14. OSGOOD, E. E., *et al.*: J. Lab. and Clin. Med., 24, 905, 1939.
15. ROURKE, M. D., and ERNSTENE, A. C.: J. Clin. Invest., 8, 545, 1930.
16. RUBIN, E. H., and SMITH, N. H.: Arch. Int. Med., 39, 303, 1927.
17. SCHUSTER, N. H.: Tubercle, 19, 529, 1938.
18. WALTON, A. C. R.: J. Lab. and Clin. Med., 18, 711, 1933.
19. WESTERGREN, A.: Acta. med. Scandinav., 54, 247, 1921.
20. WESTERGREN, A.: Ergebn. d. inn. Med. u. Kinderheilk., 26, 577, 1924.
21. WESTERGREN, A., THEORELL, H., and WIDSTRÖM, G.: Ztschr. f. exp. Med., 75, 668, 1931.
22. WINTROBE, M. M.: Am. J. Clin. Path., 11, 562, 1941.
23. WINTROBE, M. M., and LANSBERG, J. W.: AM. J. MED. SCI., 189, 102, 1935.

#### EXPERIMENTS ON COMPONENTS A AND B (QUICK) OF PROTHROMBIN

BY WILLIAM J. ONEAL, M.D.\*

ASSISTANT RESIDENT SURGEON

AND

CONRAD R. LAM, M.D.

ASSOCIATE SURGEON

DETROIT, MICH.

(From the Division of General Surgery of the Henry Ford Hospital)

In 1943, Quick<sup>1</sup> observed that if stored human plasma and plasma from a dicumarolized dog, each having a low prothrombin level as measured by the Quick test, were combined in equal amounts, the resulting mixture showed a remarkable restoration of prothrombin activity. It was his hypothesis that prothrombin must be a complex of at least 2 factors, component A which disappears from stored blood or plasma and component B which becomes low during dicumarol administration. A clinical application of this discovery was at hand.

\* Now Lt. (j. g.) USNR.

If hemorrhage or other emergency made it imperative to restore the prothrombin level in a dicumarolized patient, stored blood or plasma should be as effective as the fresh.

It seemed desirable to repeat and amplify the experiments of Quick with several significant changes in the procedure which would make the experiments *in vitro* more comparable to the proposed clinical treatment. Quick's experiments involved a heterogeneity of species; *i. e.*, human stored plasma was mixed with the dog's dicumarolized plasma. After corroborating his findings (Group 1 experiments described below) we varied the experiment by mixing stored human plasma with dicumarolized human plasma (Group 2 experiments) and mixing the corresponding plasmas of the dog (Group 3 experiments). Furthermore, in his original tests Quick used plasma from blood in which sodium oxalate had been used as the anticoagulant. Since ordinary blood bank plasma contains an excess of sodium citrate to prevent clotting, it remained to be seen if it had the same restorative effect as oxalated plasma (Group 4 experiments).

In this investigation, the usual Quick prothrombin test was performed, using rabbit brain thromboplastin.<sup>2</sup> In a small test tube are placed 0.1 cc. of plasma and 0.1 cc. of thromboplastin solution. The tube is put in a water bath at 37° C. and 0.1 cc. of 0.025 M calcium chloride is added. The time from this addition to the formation of the clot is measured with a stop watch. From an empirically constructed curve, the prothrombin concentration in per cent of normal may be estimated from the prothrombin time.

*Group 1 Experiments.* This is the original experiment of Quick, involving the combination of human stored and dog dicumarolized plasmas. In Table 1, it may be seen that his results were duplicated.

TABLE 1.—MIXTURE OF STORED HUMAN PLASMA AND DICUMAROLIZED DOG PLASMA

	Prothrombin time in sec.	% of normal
Experiment 1:		
(a) Human plasma, stored 10 days . . . . .	32	25
(b) Dog plasma, after feeding dicumarol . . . . .	22	35
Equal parts of (a) and (b) . . . . .	11	<100*
Experiment 2:		
(a) Human plasma, stored 37 days . . . . .	120	>1
(b) Dog plasma, after feeding dicumarol . . . . .	28	20
Equal parts of (a) and (b) . . . . .	12	<100*

\* Calculated on the basis of human plasma.

*Group 2 Experiments.* In these experiments, human dicumarolized plasma was substituted for the dog plasma of the preceding group. Experiments 3 and 4 reported in Table 2 are typical of 7 performed. In Experiment 5, fresh human plasma as well as stored plasma was used.

*Group 3 Experiments.* In these experiments, stored dog plasma was mixed with dicumarolized dog plasma. It was found that component A of prothrombin in the dog is much more stable than it is in man. When this plasma was stored, the prothrombin time remained approximately normal for 4 weeks, after which it became prolonged and was usually infinity at the end of 8 weeks. In Table 3, it is seen that

in Experiment 7, the combination of the 2 dog plasmas, each having an apparent prothrombin concentration of zero, resulted in a mixture with a prothrombin time of 12 seconds (60%).

TABLE 2.—MIXTURE OF HUMAN STORED AND DICUMAROLIZED PLASMAS

	Prothrombin time in sec.	% of normal
Experiment 3:		
(a) Human plasma stored 8 days . . . . .	38	20
(b) Human dicumarolized plasma . . . . .	32	15
Equal parts of (a) and (b) . . . . .	20	65
Experiment 4:		
(a) Human plasma stored 27 days . . . . .	40	5
(b) Human dicumarolized plasma . . . . .	25	30
Equal parts of (a) and (b) . . . . .	18	70
Experiment 5:		
(a) Fresh human plasma . . . . .	13	100
(b) Human plasma stored 14 days . . . . .	36	20
(c) Human dicumarolized plasma . . . . .	45	5
Equal parts of (a) and (c) . . . . .	16	70
Equal parts of (b) and (c) . . . . .	16	70

TABLE 3.—MIXTURE OF STORED AND DICUMAROLIZED PLASMAS OF THE DOG

	Prothrombin time in sec.	% of normal
Experiment 6:		
(a) Dog plasma stored 51 days . . . . .	∞	0
(b) Dicumarolized dog plasma . . . . .	29	20
Equal parts of (a) and (b) . . . . .	15	50
Experiment 7:		
(a) Dog plasma stored 64 days . . . . .	∞	0
(b) Dicumarolized dog plasma . . . . .	∞	0
Equal parts of (a) and (b) . . . . .	12	60

TABLE 4.—EFFECT OF CITRATED PLASMA

	Prothrombin time in sec.	% of normal
Experiment 8:		
(a) Fresh human plasma, citrated . . . . .	15	100
(b) Citrated human plasma, stored 3 mos. . . . .	∞	0
(c) Dicumarolized human plasma . . . . .	25	30
Equal parts of (a) and (c) . . . . .	18	65
Equal parts of (b) and (c) . . . . .	18	65
Experiment 9:		
(a) Fresh human plasma, citrated . . . . .	13	100
(b) Citrated human plasma, stored 3½ mos. . . . .	∞	0
(c) Dicumarolized human plasma . . . . .	45	5
Equal parts of (a) and (c) . . . . .	18	65
Equal parts of (b) and (c) . . . . .	18	65

*Group 4 Experiments.* The anticoagulant used in the plasmas in the above experiments was sodium oxalate, 0.5 cc. of 0.1 M sodium oxalate being used for each 4.5 cc. of blood. Blood taken for the Henry Ford Hospital blood bank is kept fluid by adding 100 cc. of 2.5% sodium citrate to 500 cc. of blood. It seemed desirable to repeat the experiments using such citrated human blood. In a number of preliminary tests, it was found that when either of the above anticoagulants was used, identical prothrombin times were obtained from the resulting plasmas. The experiments detailed in Table 4 were then carried out. Citrated plasma, stored 3 months or longer was as efficacious as fresh plasma in the restoration of dicumarolized plasma.

**Summary.** 1. The experiments of Quick which suggested the hypothesis that prothrombin consists of at least 2 components have been corroborated and amplified.

2. The combination of equal volumes of stored human plasma and plasma from a dicumarolized person gives a mixture with a Quick prothrombin level of from 60 to 70% of normal. The same is true of the corresponding plasmas of the dog.

3. Fresh human plasma was not superior to stored plasma in such restoration of prothrombin.

4. The presence of sodium citrate in excess (as in blood bank plasma) did not affect this restorative property.

#### REFERENCES

1. QUICK, A. J.: *Am. J. Physiol.*, 140, 212, 1943.
2. QUICK, A. J.: *Am. J. Physiol.*, 114, 283, 1936.

## HEMOLYTIC TRANSFUSION REACTIONS DUE TO THE Rh FACTOR

### REPORT OF 2 CASES

By CAPT. ARTHUR W. FRISCH, M.C., A.U.S.

LABORATORY SECTION, PERCY JONES GENERAL AND CONVALESCENT HOSPITAL\*

THE present conception of atypical agglutinins as a cause of transfusion reactions originates from the significant observations made by Levine and Stetson in 1939.<sup>1</sup> They described an antibody, responsible for a transfusion reaction, which agglutinated 80% of human Group O bloods and which was "independent of the M, N and P factors." Moreover, Levine and Stetson recognized the clinical significance of their findings and pointed out that beneficial transfusions could be obtained by the proper selection of donors whose cells failed to react with the atypical agglutinin; and that the immunization of the mother in their case was due to fetal tissues inherited from the father. These studies, together with the discovery of the Rh factor by Landsteiner and Wiener, and the detection of atypical antibodies in cases of repeated transfusions<sup>4,11</sup> have stimulated renewed interest in reactions following the infusion of blood. Patients with various blood dyscrasias are commonly given numerous transfusions over an extended period of time so that adequate opportunity for iso-immunization exists. Reactions are believed to occur more frequently in this group,<sup>4</sup> but careful investigation often fails to reveal an appropriate cause. The purpose of this report is to present 2 cases in which proof was obtained that the Rh factor was responsible for the transfusion reactions.

The first patient, H, was a 24 year old white male with far-advanced Hodgkin's disease, belonging to the blood Group O, Type Rh negative. From June 9 to June 27, 1944, while in another general hospital, he received 4 transfusions without reaction. On July 1 an infusion of

\* Now stationed at the School of Public Health, University of Michigan, Ann Arbor, Mich.

washed red blood cells resulted in hives and dyspnea; this was followed by icterus, which, however, persisted and may have been due to hepatic metastases already known to exist. He was admitted to this hospital on July 5, 1944. During the following 15 days he was given 4 transfusions of citrated blood and 2 red cell infusions. With each of these he experienced reactions which consisted of chill, usually developing 1 to 2 hours after transfusion, and fever ranging from 101.4° to 104.4° (Table 1). On one occasion (July 20) hemoglobinuria followed a severe chill. All bloods given were "compatible" as judged by carefully performed cross-matchings using the test-tube technique recommended by Levine *et al.*<sup>2</sup> The data in Table 1 summarize the clinical and laboratory results on the donors used for transfusion.

TABLE 1.—TRANSFUSIONS, PATIENT H

Date 1944	Reaction	Donor	Agglutination of donors' cells by serum	
			Anti-Rh	Patient H (7-29)
7-7 . .	Chill, temp. 104.4°	O	+	+
7-8 . .	Chill, temp. 103.4°	O	Unkn.	Unkn.
7-11 . .	None	O	+	+
7-14 . .	Chills, temp. 101.4°	O	Unkn.	Unkn.
7-20 . .	Chill, temp. 103°, hemoglobinuria	O	+	+
7-22 . .	None	O	+	+
8-3 . .	None	O	-	-
8-11 . .	None	O	-	-
8-17 . .	None	O	-	-
8-23 . .	None	O	-	-

One week following a transfusion (July 22) a warm agglutinin was detected in the serum of Patient H which was tested with 127 known bloods of all groups.\* When the figures were corrected for the frequency of the Rh factor in the population at large (85%), the reactions corresponded closely with a serum first described by Levine *et al.*<sup>2</sup> and designated as anti-Rh<sub>1</sub> by Wiener, Sonn and Belkin.<sup>12</sup> This antibody is characterized by the fact that it agglutinates the blood of approximately 70% of white individuals of New York City and by the fact that it clumps a small number of bloods (Rh') which fail to agglutinate with standard anti-Rh serums. The serum from Patient H agglutinated 69% (corrected figure) of the bloods tested. Among these were 5 individuals characterized as Rh negative with the standard 85% serum obtained from Dr. Levine.

The second patient, Z, was a white male, age 22, admitted to this hospital Nov. 15, 1943, with a diagnosis of aplastic anemia. At other stations he had received a total of 5 transfusions from October 5 to November 10 without reaction. At this hospital, between January 3 and March 15, he received 10 transfusions, at least 5 of which were Rh-positive bloods. Only minor reactions were noted. On July 8 his anemia became more pronounced and transfusion therapy was again resumed after an interval of nearly 4 months. In the next 4 days he had severe reactions to only small quantities of blood, sub-

\* The A and B substance of Witebsky, used to inactivate the isohemagglutinins, was obtained through the generosity of the Eli Lilly Company.



sequently found to be Rh positive (Table 2). At the same time the recipient was tested and found to be Rh negative. However, we were unable to demonstrate Rh antibodies in his serum and cross-tests with known Rh-positive cells were thoroughly compatible *in vitro* at 37° and at ice-box temperature. Nevertheless we proceeded to give him only Rh-negative blood on empiric grounds. From July 13 to August 8 he received 13 transfusions with only 2 minor febrile reactions. During this period the patient's serum was investigated for the presence of atypical antibodies without success. Since our supply of Rh-negative donors was limited and since we had no actual proof that the Rh factor was involved,\* it was decided to attempt once more an infusion with

TABLE 2.—TRANSFUSIONS, PATIENT Z

Date	Reaction	Donor's group	Type Rh
1-3 . .	None	A	+
1-7 . .	None	A	-
1-12 . .	Chill, 101°	A	+
1-26 . .	None	A	+
2-2 . .	None	A	-
2-8 . .	None	A	Unkn.
2-15 . .	None	A	Unkn.
2-22 . .	None	A	+
3-4 . .	None	A	Unkn.
3-15 . .	Chill, 102°	A	+
7-8 . .	250 cc., chill, vomiting, 102.8°	A	+
7-11 . .	175 cc., chill, 101.6°	A	+
7-12 . .	200 cc., chill, 102°	A	+
7-13 . .	None	O	-
7-14 . .	None	O	-
7-15 . .	None	O	-
7-19 . .	None	A	-
7-20 . .	101.6°	A	-
7-21 . .	None	A	-
7-22 . .	None	A	-
7-24 . .	101.2°	A	-
7-25 . .	None	A	-
7-26 . .	None	A	-
7-27 . .	None	A	-
8-5 . .	None	A	-
8-8 . .	None	A	-
8-11 . .	Vomiting, jaundice, hemoglobinuria, 104.6°	A	+
8-16 . .	None	A	-
8-22 . .	None	A	-
8-23 . .	None	A	-
8-24 . .	None	A	-

Rh-positive blood. Transfusion was started at approximately 3:30 P.M. on Aug. 11, 1944; when 200 cc. had been infused, signs of beginning reaction became evident in the form of headache, nausea and malaise. These symptoms grew progressively more severe, until the headache was intense and vomiting occurred. The transfusion (500 cc.) was completed at about 6:00 P.M., at which time the patient was found to have a temperature of 104.8° F., although he stated that he did not feel especially warm and had had no real chills. Later in the evening the patient appeared markedly toxic and weak and experienced severe

\* There was some suspicion of pyrogens in transfusion sets at that time.

bouts of nausea and vomiting. On the following morning icterus was apparent (icterus index 64) and his urine contained some red cells and a large amount of free hemoglobin. Alkalies and fluids were promptly administered and a satisfactory output of urine was obtained. The icterus diminished rapidly and the hemoglobinuria disappeared within 24 hours. The hemorrhagic phenomena and underlying thrombocytopenia were apparently little affected by the transfusion reaction.

A specimen of blood from this patient was examined only 4 hours after transfusion and we were unable to demonstrate the presence of the Rh-positive cells. Similar negative results were obtained the following day. This observation was not surprising in view of the subsequent serologic findings and the rapidity with which jaundice and hemoglobinuria developed. The patient's serum was then tested for "blocking antibodies" of the type recently reported by both Wiener<sup>7</sup> and Race.<sup>3</sup> Z's serum, 0.2 cc. of varying dilutions, was incubated for 1 hour at 37° C. with 1 drop of a 2% suspension of Rh-positive cells. One drop of an appropriate dilution of anti-Rh serum was then added to each tube; the mixtures were again incubated for 1 hour at 37° C. and examined for agglutination. Appropriate control sera from negative unsensitized individuals failed to inhibit the Rh agglutination reaction.

TABLE 3.—Rh BLOCKING TEST—PATIENT Z'S SERUM

	Date 1944	Dilutions of serum									
		15	20	30	40	60	80	120	160	240	320
1	8- 5	—	—	—	—	—	—	—	++	++	++
2	8- 8	—	—	—	—	—	—	—	++	++	++
3	8-11*	—	—	—	—	+	++	++	++	++	++
4	8-12	—	—	—	—	+	++	++	++	++	++
5	8-14	—	—	—	—	++	++	++	++	++	++
6	8-16	—	—	—	—	—	—	—	++	++	++
7	8-19	—	—	—	—	—	—	—	+	++	++
8	8-23	—	—	—	—	—	—	—	++	++	++

\* Serum obtained 4 hours after transfusion with Rh positive blood.

It should be noted (Table 3) that 6 days prior to transfusion the serum of Patient Z contained Rh-inhibiting antibodies to a titer of 1:120. Four hours following transfusion (August 11) and for 3 days thereafter the titer was reduced to 1:60; this in turn was followed by a subsequent restoration to the former level (August 16). At no time were agglutinating antibodies demonstrable in the patient's serum. The drop in titer following infusion of Rh-positive blood was regarded as evidence of the union of donor cells and antibody *in vivo*.

**Discussion.** Patient H in whom agglutinating antibodies of Type Rh<sub>1</sub> were demonstrable, exhibited several characteristic features of acquired iso-immunization. A succession of transfusions was required before evidences of transfusion reaction appeared and these became progressively more pronounced, finally terminating in frank hemoglobinuria. As Wiener has pointed out, hemolysis due to Rh incompatibility may be at first not apparent but may eventually result in a severe or fatal reaction.<sup>6</sup> Appropriate examinations of blood from

Patient H, utilizing the factors M and N as an index of the destruction of donor cells, may have aided us in avoiding the acute reaction of July 20 and the risk of serious outcome.<sup>6,11</sup> The development of symptoms probably due to the Rh factor within a month after the initial transfusion is a shorter time than usually required for iso-immunization. However, Vogel, Rosenthal and Levine<sup>4</sup> reported a case (No. 4) in which only 8 transfusions and an interval of  $1\frac{1}{4}$  months was adequate for the development of anti-Rh agglutinins.

The specificity of the antibody in Patient H is of some interest inasmuch as its relationship to the Rh factor was at first obscured by the fact that it reacted with some Rh-negative bloods.<sup>2</sup> A serum giving somewhat similar reactions was also reported by Wiener<sup>6</sup> from a case involving multiple transfusions and subsequently classified as anti-Rh<sub>1</sub> by Wiener and Landsteiner.<sup>10</sup> It is of interest to note that the blood cells of all Rh-positive donors tested (Table 1) were agglutinated by the serum of Patient H, indicating that they belonged to the sub-types Rh<sub>1</sub> or Rh<sub>1</sub>Rh<sub>2</sub>.<sup>12</sup> On the basis of the distribution of the Rh<sub>1</sub> type which occurs in 50%, in contrast to the Rh<sub>2</sub> type which is found in only 15.5% of the general population, it is to be expected that the anti-Rh<sub>1</sub> iso-immunization would occur more frequently than the anti-Rh<sub>2</sub>. Only recently Waller, Levine and Garrow reported a case of erythroblastosis fetalis involving the Rh<sub>1</sub> factor in which the mother of the baby was Rh<sub>2</sub>.<sup>5</sup> Additional cases of iso-immunization of Rh-positive mothers of Type Rh' have been described by Levine, Burnham, Katzin and Vogel,<sup>2</sup> and by Wiener.\*<sup>8</sup>

The second patient, Z, is also of special interest because of the high titer of Rh blocking antibodies present in his serum despite the absence of demonstrable agglutinating antibodies. This finding confirms the observation of Wiener<sup>7</sup> regarding the development of inhibiting (non-agglutinating) factors in sera of patients sensitized to the Rh antigen. Since only 2% of Rh-negative individuals respond by producing agglutinins to the Rh factor following multiple transfusions,<sup>9</sup> the demonstration of an inhibiting antibody is of considerable value as a method of detecting Rh sensitization where agglutinating antibodies are not present in the circulation.<sup>4,6</sup> We have recently had the opportunity to apply the blocking test in 2 cases of iso-immunization during pregnancy which resulted in erythroblastic infants. Both mothers were Rh negative and the fathers Rh positive. Interval tests during the period following delivery failed to reveal the presence of Rh agglutinins. Blocking antibodies, however, were present in a titer of 1:2 in 1 case and 1:16 in the other. One additional case is worthy of mention. This patient was an O, Rh-negative male with suppurative pulmonary disease who received 24 transfusions over a period of  $1\frac{1}{2}$  years with no reactions whatsoever. On Aug. 17, 1944, two 500 cc. transfusions using O, Rh-positive donors were given with benefit and without reaction. One month later the recipient's serum was tested but Rh agglutinins were not demonstrable. Tests for blocking antibody, however, were positive to a titer of 1:4. In view

\* See for additional references.

of the above findings this patient, although sensitized to the Rh factor, was apparently able for some unknown reason, to receive Rh-positive blood with impunity.

**Summary.** Two cases of severe reactions following multiple transfusions were found to be due to the Rh factor. In 1 patient an atypical agglutinin conforming to the sub-type Rh<sub>1</sub> was demonstrable. In the second, the Rh antigen was implicated by finding a high titer of "blocking" antibodies in the recipient's serum despite the absence of agglutinins.

#### REFERENCES

1. LEVINE, P. H., and STETSON, R. E.: An Unusual Case of Intra-Group Agglutination, *J. Am. Med. Assn.*, **113**, 126, 1939.
2. LEVINE, P. H., BURNHAM, L., KATZIN, E. M., and VOGEL, P.: The Role of Isoimmunization in the Pathogenesis of Erythroblastosis Fetalis, *Am. J. Obst. and Gynec.*, **42**, 925, 1941.
3. RACE, R. R.: An "Incomplete" Antibody in Human Serum, *Nature*, **153**, 771, 1944.
4. VOGEL, P., ROSENTHAL, P., and LEVINE, P. H.: Reactions as a Result of Isoimmunization Following Repeated Transfusions of Homologous Blood, *Am. J. Clin. Path.*, **13**, 1, 1943.
5. WALLER, R. K., LEVINE, P. H., and GARROW, I.: A Case of Erythroblastosis Caused by Immunization Through the Rh Factor in an Rh Positive Mother (in press).
6. WIENER, A. S.: Hemolytic Reactions Following Transfusions of Blood of the Homologous Group, II: Further Observations on the Role of the Property Rh, Particularly in Cases Without Demonstrable Isoantibodies, *Arch. Path.*, **32**, 227, 1941.
7. WIENER, A. S.: A New Test (Blocking Test) for Rh Sensitization, *Proc. Soc. Exp. Biol. and Med.*, **56**, 173, 1944.
8. WIENER, A. S.: Role of the Subtypes of Rh in Hemolytic Transfusion Reactions and in Erythroblastosis, *Am. J. Clin. Path.*, **14**, 52, 1944.
9. WIENER, A. S.: The Nature of the Rh Agglutination Reactions, *Science*, **100**, 98, 1944.
10. WIENER, A. S., and LANDSTEINER, K.: Heredity of Variants of the Rh Type, *Proc. Soc. Exp. Biol. and Med.*, **53**, 167, 1943.
11. WIENER, A. S., and PETERS, R. H.: Hemolytic Reactions Following Transfusions of Blood of the Homologous Group, With Three Cases in Which the Same Agglutinin Was Responsible, *Ann. Int. Med.*, **13**, 2306, 1940.
12. WIENER, A. S., SONN, E. G., and BELKIN, R. B.: Heredity of the Rh Blood Types, *J. Exp. Med.*, **79**, 235, 1944.

## THE ACCEPTABILITY AND EFFECTIVENESS OF THE CONDOM AS A CONTRACEPTIVE METHOD\*†

BY CHRISTOPHER TIETZE, M.D.

BALTIMORE, MD.

AND

JOHN B. HAGAMAN, M.D.

BOONE, N. C.

INSTRUCTION in contraception has an important place in any complete public health program. Its importance in cases where pregnancy is contraindicated is well recognized. Of almost equal importance is its use to prevent unduly frequent pregnancies with their unfavorable effect upon mother and child. While the diaphragm-and-jelly method is considered very reliable, its general introduction in the public health

\* From the National Committee on Maternal Health, 2 East 103rd St., New York City.

† Thanks are due the Johns Hopkins University School of Hygiene and Public Health for space and assistance in preparing this report.

field has been limited by the amount of the physician's time required for fitting and the details of instruction. For this reason the simpler methods are capable of much wider application. Of these, only foam-powder-and-sponge<sup>2,3</sup> and jelly-alone<sup>4,5,6,9</sup> have been widely studied.

Technical improvements of the past decade have produced condoms which, being thinner and more carefully inspected for holes and other defects than previously, interfere less with sensation during intercourse, are more durable, and promise a higher degree of protection than earlier sheaths. *A priori* they would seem well adapted to use in public health programs. They have not, however, been tested on a large scale in a controlled experiment.

To secure an estimate of the acceptability and effectiveness of condoms under conditions closely resembling those of a public health program, a series of carefully studied cases were planned by Dr. Gilbert W. Beebe under the auspices of the National Committee on Maternal Health. Condoms of an assured high quality (Trojans) were supplied by the Youngs Rubber Corporation. They had been tested by the manufacturer by being mechanically stretched over a blunt metal cylinder whose diameter was 1.5 times that of the condoms when flaccid. When dipped in a solution of a neutral wetting agent, holes were indicated by a ring of fluid beneath the rubber, and any such condom was rejected. This technique appeared superior to the earlier practices of inflation and visual inspection. Because of it and in order to keep the procedure as simple as possible, further testing by the user was not suggested.

A rural area where the population had been little exposed to education in matters of birth control was found in Watauga County, N. C. To make the results applicable to situations where little or no physician's time would be available, the physician in charge (J. B. H.), after choosing the patients in need of pregnancy spacing, directed a registered nurse, Lena Gilliam Hillard, R.N., to give the instructions. She was peculiarly well-fitted for the work, being a native of a similar region in Kentucky and having assisted at Berea in a test of the acceptability and effectiveness of jelly-alone.<sup>5</sup> As the work progressed it became evident that the families for whom the physician had prescribed the service comprised a major portion of the rural farm population. Therefore, in order to approach the statistically desirable ideal of an unselected population, he instructed the nurse to offer the same service to all couples.

As the county contained more rural-farm families than could be included in the program, representative geographical selection was secured by subdividing it into 26 areas bounded by roads, and choosing 13 of these at random. Although service was given to a few colored couples, the present analysis has been limited to whites to secure a more homogeneous material. To avoid inclusion of a large number of women past menopause, those above the age of 45 years were likewise eliminated. The population studied, accordingly, comprises all the married white rural-farm women under 45, living in the 13 areas constituting approximately half of Watauga County.

At the first visit the need for birth control was discussed with the wife and the use of the condoms explained. If the free supply of these was accepted, a dozen condoms were left. Those who accepted the service were revisited 2 weeks later. If at this visit the condoms had not proved satisfactory, the nurse was instructed to make suggestions for better use of the sheaths, such as the use of a lubricant. If it was found that both wife and husband were satisfied with the method, a larger supply was given and further follow-up visits were made at intervals of about 6 months. Repeated use of each sheath was not suggested.

The history taken at the initial visit provided a record, as accurate as the patient's memory permitted, of the exposure to pregnancy and of the use or non-use of contraception for each month of her married life, as well as of each pregnancy and its termination. At every follow-up visit this information was brought up to date. All patients were followed until they decided to abandon the service or until they left the county. The present analysis covers the first 4 years of the project, from its onset in September 1939 to late in 1943. During the later part of this period a certain proportion of the follow-up work with the more intelligent and coöperative patients was carried out at the nurse's office in Boone or by mail.

Although a considerable number of women became accustomed to write for supplies, it should be clearly understood that the main initiative and responsibility for the continuation of the service rested at all times with the physician and the nurse. For many of the participants the service remained something which was brought to them without effort on their part rather than something they went out of their way to obtain.

A total of 658 married couples were found in the survey area who fulfilled the conditions listed above. The mean age of the wives was 29.3 years, the mean duration of marriage 10.3 years. The occupation of 83% of the husbands was recorded as farmer, the others being a miscellaneous group, including laborers, mill workers, carpenters, mechanics, mail carriers, storekeepers, and a few teachers and ministers. Of the families, 17% had received some relief during the year. The median number of school years completed was 7.8 for the husbands and 8 for the wives. The average number of children ever born per marriage was 3.2. Contraceptive techniques (including withdrawal) had been used by 45% of all couples, and were being used at the time of the interview by 38%. Of the 249 couples practicing contraception, 65% were using condoms, 17% withdrawal, 5% douches, with jellies, suppositories, safe period and diaphragm, each accounting for 2% or less.

Human fecundity and the efforts to control it are most adequately studied in terms of pregnancy rates "per 100 years of exposure." For this purpose the duration of exposure is computed by deducting from the total months of married life under consideration those during which conception cannot occur because of pregnancy, abstinence, separation and the like. The pregnancy rate per 100 couples per year

of exposure or, for conciseness, per 100 years of exposure, is calculated by the formula:

$$\text{Pregnancy rate} = \frac{\text{Total number of conceptions}}{\text{Total months of exposure}} \times 1200$$

It is necessary to distinguish periods of exposure without and with resort to contraception. The pregnancy rate per 100 years of exposure is higher for the period before the first pregnancy than afterwards, because later exposure includes months of postpartum amenorrhea and lactation during which the risk of pregnancy is reduced. Previous investigators have reported rates from 112 to 271 for first pregnancies and from 70 to 105 for second and subsequent pregnancies, when no contraception was used.

Since the majority of studies of his type have been made in connection with birth control clinics, the terms "pre-clinic" and "post-clinic" have come into general use. For this reason they will be employed here, although no clinic in the conventional sense was operated in Watauga County and the terms "pre-interview" and "post-interview" perhaps would be technically more correct. During the pre-clinic period, while no contraception was being used, those who accepted supplies had a pregnancy rate of 125 per 100 years of exposure for first pregnancies and of 64 for later pregnancies. That their untutored efforts at birth control had been effective is shown by a rate of only 13 pregnancies per 100 years of exposure for periods when contraception was used after the termination of the first pregnancy.

From the point of view of usefulness in public health work, the acceptability of a method is of great importance. The first measure of this, the proportion of those to whom condoms are offered who will try them, depends on many imponderable elements, such as the personality of the individual making the offer, the religious background and educational status of the couples, their previous experience with the condom or other contraceptive methods, and many others. For the couples who were already using condoms at the time of the first interview, the proportion who accepted the supplies was understandably high, amounting to 91%. For those who were using other methods and for those not using contraception, the proportions were almost identical, being 49 and 48% respectively, and 59% for all wives interviewed. Of the 271 refusing the service, 28% felt they did not need it because of natural or operative sterility. Twenty-five per cent stated they had religious or moral objections and 13% wanted a baby as soon as possible.

An even more important measure of acceptability is the proportion of those who accepted and tried the supplies who were still using condoms after varying lengths of time. This proportion amounted to 85, 79 and 73% after 1, 2 and 3 years, surprisingly high figures in view of the current clinical opinion that the male will not long tolerate the interference with sensation. The proportions were somewhat higher, as may be expected, for those who were using condoms at the time of the first interview, lower for those who were not practicing

contraception at that time, and lowest for those using other methods, being 81, 71 and 61 % respectively, at the end of 3 years.

Taken as a whole, the acceptability of the condom in terms of continued use seems to be relatively high in comparison with the published findings for other contraceptives.<sup>2,5,6,10</sup> This comparison, however, can only be made in a general way because of the differences in investigative technique. Furthermore, the readiness with which couples may obtain materials and instruction for other methods varies from group to group. It should also be emphasized that the high ratios of continued use were obtained under the stimulus of home visits by the nurse at regular intervals. It seems probable that a mode of distribution requiring greater initiative and effort from the participants would have been less successful.

As might be expected, the complaint of "interference with sensation" was the most frequent one given as a reason for discontinuing the use of condoms. Among couples who stopped in spite of continuing exposure to the risk of pregnancy, this reason was recorded in two-fifths of the classifiable cases. In 44 instances the discontinuance could be definitely attributed to one of the spouses, 38 times to the husband and 6 times to the wife.

The post-clinic pregnancy rate shows a marked reduction from that before the patients had been given condoms. In a total of 649 years of exposure to the risk of pregnancy, 72 conceptions occurred, corresponding to a rate of 11 per 100 years. The same rate was found when first pregnancies were left out of consideration. This includes all unplanned conceptions before the method had been definitely and permanently discontinued, even those occurring after the patient had run out of supplies or after other irregular use. To determine the rate which would have resulted had the method been used according to instructions on every occasion is impossible, because it is evident from the records that irregular use was in many instances only admitted after conception had taken place. An approach to the appraisal of "physiologic effectiveness" is suggested by the fact that irregular use was admitted for three-fourths of the unplanned conceptions, and even more by the observation that of pregnancies terminated prior to the closing of the records, four-fifths were followed by resumption of condom use. Ten of the pregnancies were alleged to have followed an occasion on which the condom was found to have broken. In only 9 cases of unplanned pregnancy out of the total of 72 was perfect use on every occasion claimed.

Those with previous experience in some form of birth control were found to be more successful in limiting conceptions after receiving condoms, having a post-clinic rate of 6 second-and-subsequent pregnancies per 100 years of exposure compared with one of 16 for those who had never previously practiced contraception.

Comparisons with the physiologic effectiveness of other methods are difficult, since no two populations can be assumed to have the same degree of skill and regularity in the use of a method. The results secured in Watauga County, when compared with other reports



(Table 1), show that, under conditions of actual use, the effectiveness of the condom surpassed that of jelly-alone and of foam powder-and-sponge and almost reached that of diaphragm and jelly. When the rate of 6 for those with previous contraceptive experience is considered, it is seen to equal the lowest rate previously reported, one secured with diaphragm and jelly in a private practice composed chiefly of college-trained women from upper-middle-class homes.<sup>8</sup>

TABLE 1.—COMPARISON OF PREGNANCY RATES PER 100 YEARS OF EXPOSURE\* DURING USE OF CLINICALLY PRESCRIBED CONTRACEPTIVES

Method and residence	Years of exposure	Pregnancies	
		No.	Rate
<b>Diaphragm and jelly:</b>			
Philadelphia <sup>8</sup> . . . . .	935	59	6
Port Chester, N. Y. <sup>1</sup> . . . . .	472	32	7
New York City <sup>10</sup> . . . . .	703	65	9
Cincinnati <sup>10</sup> . . . . .	2703	244	9
Nashville <sup>2</sup> . . . . .	361	32	9
Spartanburg, S. C. <sup>10</sup> . . . . .	671	87	13
<b>Condom:</b>			
Watauga County . . . . .	604	68	11
<b>Foam powder-and-sponge:</b>			
Urban Florida <sup>7</sup> . . . . .	377	103	27
Nashville <sup>2</sup> . . . . .	206	57	28
New York City <sup>11</sup> . . . . .	82	29	35
<b>Jelly-alone:</b>			
Philadelphia <sup>4</sup> . . . . .	60	9	15
New York City <sup>7</sup> . . . . .	203	33	16
Chicago <sup>9</sup> . . . . .	241	47	20
Rural Kentucky <sup>5</sup> . . . . .	204	41	20
Logan County <sup>6</sup> . . . . .	938	354	38

\* Chiefly for second and subsequent pregnancies.

Since the acceptability and effectiveness of condoms were found to exceed those indicated by current clinical opinion, it would appear that this contraceptive method is capable of much wider application in the public health field than has hitherto been made. The time required for instruction is short and this portion of the consultation can be delegated to a nurse. Although the method is primarily one for the use of the husband, it has been shown that instruction can be given satisfactorily through the wife.

**Summary and Conclusion.** 1. Under conditions closely resembling those of a public health program, condoms were offered by a registered nurse, under the supervision of a physician, to married women requiring pregnancy spacing. Subsequently the service was extended to include all married women living on farms in half of Watauga County, N. C.

2. Supplies were accepted and used by 59% of the couples.

3. Of those who tried the condoms, 73% were still using them after 36 months.

4. The post-clinic pregnancy rate was 11 per 100 years of exposure, including cases of irregular use. The protection approximated that reported for diaphragm-and-jelly and exceeded that afforded by foam powder-and-sponge and by jelly-alone.

5. The prescription of condoms for the prevention of dangerous or undesirable pregnancies requires little of the physician's time and is well suited to inclusion in public health programs.

A more detailed review of the findings appears elsewhere.<sup>12</sup>

#### REFERENCES

1. BEALS, D.: A Clinical Study of Diaphragm and Jelly, *J. Contracept.*, **3**, 77, 1938.
2. BEEBE, G. W., and OVERTON, J.: The Contraceptive Service of the Department of Health, City of Nashville, *J. Am. Med. Assn.*, **118**, 1045, 1942.
3. BEEBE, G. W., and BELAVAL, J. S.: Fertility and Contraception in Puerto Rico, Puerto Rico J. Pub. Health and Trop. Med., **18**, 3, 1942.
4. BEEBE, G. W., and GAMBLE, C. J.: Clinical Contraceptive Results in a Small Series of Patients, *J. Am. Med. Assn.*, **115**, 1451, 1940.
5. BEEBE, G. W., and GEISLER, M. A.: Control of Conception in a Selected Rural Sample, *Human Biol.*, **14**, 1, 1942.
6. BEEBE, G. W.: Contraception and Fertility in the Southern Appalachians, Baltimore, Williams and Wilkins, pp. 277, 1942.
7. BEEBE, G. W.: Unpublished material quoted from Reference 5.
8. DEWEES, L., and BEEBE, G. W.: Contraception in Private Practice, *J. Am. Med. Assn.*, **110**, 1169, 1938.
9. STEIN, I. F., COHEN, M. R., and NIELSEN, R.: Jelly Alone as a Contraceptive Method, *Human Fertility*, **7**, 33, 1942.
10. STIX, R. K.: Contraceptive Service in Three Areas, Part II. The Effectiveness of Clinic Services, *Milbank Memorial Fund Quart.*, **19**, 304, 1941.
11. STONE, H. M.: Clinical Experiences With the Foam Powder Method, *J. Contracept.*, **3**, 3, 1938.
12. TIETZE, C., and GAMBLE, C. J.: The Condom as a Contraceptive Method in Public Health Work, *Human Fertility*, **9**, 97, 1944.

---

### THE MAGNESIUM PARTITION IN HYPERTHYROIDISM WITH SPECIAL REFERENCE TO THE EFFECT OF THIOURACIL

BY GROSVENOR W. BISSELL, M.D.\*

BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services [Harvard], Boston City Hospital, and the Department of Medicine, Harvard Medical School)

SERUM magnesium is only partially ultrafiltrable in normal persons. In human blood, by ultrafiltration, Watchorn and McCance<sup>17</sup> found that the diffusible magnesium varied between 60 and 90% with an average of 80%  $\pm$  7. Recently Soffer and his associates<sup>13,15</sup> have noted in Graves' disease that, although the total serum magnesium was normal, the non-diffusible, or bound magnesium, was much increased at the expense of the diffusible fraction. Administration of Lugol's solution to the patient caused a decrease in the bound magnesium while thyroidectomy restored the levels of diffusible and non-diffusible magnesium to the normal range. In myxedema the situation was found to be reversed, all the magnesium being in the diffusible fraction. Dine and Lavietes<sup>5</sup> confirmed these findings and suggested a possible relation of bound magnesium to the thyroid hormone or to certain enzyme systems.

Cope and Wolff<sup>4</sup> reported that they were unable to find consistent differences between the levels of the bound magnesium of hyper-

\* Now at Edward J. Meyer Memorial Hosp., Buffalo, N. Y.

thyroid patients and normal individuals. They likewise reported that the effects of iodine administration and thyroidectomy on the bound serum magnesium were equivocal.

Thiouracil has been found effective in the treatment of hyperthyroidism.<sup>1,18,19</sup> This drug acts by preventing the synthesis of the thyroid hormone. While investigating the action of thiouracil in relation to various electrolytes, its effect on the serum magnesium partition was studied.

**Methods.** Blood was drawn under oil from subjects in the postabsorptive state. Serum was separated as soon as adequate clotting had occurred, since hemolysis introduces serious errors into the determination of the magnesium fractions.<sup>12</sup> Serum was usually ultrafiltered as soon as obtained. Otherwise, it was stored under oil or paraffin at 5° C. Ultrafiltrates were obtained by an anaërobic technique, employing the capsule of Lavietes.<sup>7</sup> A "450" washed cellophane membrane was employed, with an effective ultrafiltration pressure of 28 cm. mercury. All ultrafiltrations were carried out for 8 to 12 hours at room temperature. An average of 4 cc. of ultrafiltrate was obtained from about 10 cc. of serum. The total serum magnesium was determined on 2 cc. amounts of serum by the method of Briggs.<sup>2</sup> Calcium was precipitated by the method of Clark and Collip.<sup>3</sup> Phosphate was determined colorimetrically by the method of Tschopp and Tschopp.<sup>16</sup> Ultrafilterable magnesium was determined as was the total serum magnesium except that the protein precipitation of the ultrafiltrate with trichloroacetic acid was omitted. Known amounts of magnesium sulfate equivalent to 1 mg. % magnesium were carried through with each set of determinations to insure the accuracy of the method. Bound magnesium was expressed as the arithmetical difference between the total and ultrafilterable magnesium levels. Total serum protein was determined by the copper sulfate method.<sup>10</sup>

TABLE 1.—TOTAL SERUM MAGNESIUM AND THE PER CENT OF NON-DIFFUSIBLE (BOUND) MAGNESIUM IN NORMAL INDIVIDUALS

No.	Sex	Total serum magnesium (mg. per 100 cc.)	% of bound magnesium	Total protein (gm. per 100 cc.)
1 . . . . .	M	1.91	17	5.8
2 . . . . .	M	2.06	26	6.0
3 . . . . .	M	2.16	27	5.8
4 . . . . .	M	2.60	32	5.3
5 . . . . .	M	2.31	30	5.8
6 . . . . .	M	2.22	25	
7 . . . . .	M	2.24	36	6.0
8 . . . . .	M	2.55	32	
9 . . . . .	M	2.65	35	
10 . . . . .	F	2.32	42	
11 . . . . .	F	2.01	29	
12 . . . . .	F	2.06	17	5.7
13 . . . . .	F	2.16	31	5.8
14 . . . . .	F	2.21	40	5.8
15 . . . . .	F	2.15	29	
16 . . . . .	F	2.30	36	5.5
17 . . . . .	F	2.68	34	
18 . . . . .	F	2.36	29	

Mean: 2.28 ± 0.03 30.4 ± 1.1

**Results.** Total and ultrafilterable magnesium determinations were made in normal individuals, and in patients with hyperthyroidism before and during treatment with thiouracil.

Table 1 shows the results obtained in 18 normal persons, chiefly internes and technicians. There were 9 males and 9 females in the

TABLE 2.—THE TOTAL AND PER CENT OF NON-DIFFUSIBLE (BOUND) MAGNESIUM IN PATIENTS WITH HYPERTHYROIDISM; THE EFFECTS OF THIOURACIL  
 Thiouracil administered

No.	Sex	Age	Duration of illness (mo.)	Total protein (gm. p. 100 cc.)	Initial BMR	Total serum Mg. (mg./ 100 cc.)	% bound Mg	1 week			2 weeks			3 weeks			4 weeks or longer		
								BMR	Total serum Mg. (mg./ 100 cc.)	% bound Mg	BMR	Total serum Mg. (mg./ 100 cc.)	% bound Mg	BMR	Total serum Mg. (mg./ 100 cc.)	% bound Mg	BMR	Total serum Mg. (mg./ 100 cc.)	% bound Mg
1	F	43	12	5.5	+48	2.08	30	+43	2.03	25	+33	1.95	22	+16	2.11	25	+17	1.61	30
2	F	20	12	5.8	+60	1.59	25	+33	2.29*	40	0	2.06	22	..	..	..	+11	2.36	35
3	F	42	18	4.9	+53	1.67	30	+37	1.84	27	..	..	..	..	..	..	..	..	..
4	F	34	24	5.5	+56	2.04	26	+33	1.91	25	+30	2.08	29	+12	2.29	23	+12	2.08	17
5	F	35	12	5.5	+51	1.94	36	..	..	..	..	..	..	+19	1.00	36	..	..	..
6†	F	35	48	5.5	+41	1.03	47	..	..	..	..	..	..	..	..	..	..	..	..
7†	F	60	6	..	+77	2.18	44	..	..	..	..	2.12	31	..	..	..	..	..	..
8	F	54	36	5.1	+96	2.79	52	..	2.21	7	..	1.62	17	..	..	..	+11	2.24	21
9	F	28	12	5.2	+65	2.11	10	..	..	..	..	..	..	-24	1.81	20	..	1.94	27
10	F	28	3	8.5	+33	1.74	26	..	..	..	..	..	..	..	..	..	..	..	..
11	F	31	8	..	+35	1.08	9	..	..	..	..	..	..	..	..	..	..	..	..
12	F	46	5	6.4	+40	1.37	28	..	..	..	..	..	..	..	..	..	..	..	..
13	F	38	12	5.3	+34	1.96	25	..	..	..	..	..	..	..	..	..	..	..	..
14	M	35	12	5.5	+60	1.48	14	..	..	..	..	..	..	..	..	..	..	..	..
15	F	22	5	..	+50	1.22	44	..	..	..	..	..	..	..	..	..	..	..	..
16	F	26	12	5.2	+64	1.67	17	..	..	..	..	..	..	..	..	..	..	..	..
17	F	21	6	6.5	+63	2.16	36	..	..	..	..	..	..	..	..	..	..	..	..
18	F	51	12	..	+56	1.91	23	..	..	..	..	..	..	..	..	..	..	..	..
19	F	56	24	5.6	+52	1.54	5	..	..	..	..	..	..	..	..	..	..	..	..
20	F	28	5	5.2	+63	2.16	43	..	..	..	..	..	..	..	..	..	..	..	..
21	F	50	6	6.0	+57	2.06	43	..	..	..	..	..	..	..	..	..	..	..	..
22	F	54	12	5.3	+50	2.21	31	..	..	..	..	..	..	..	..	..	..	..	..
23	F	54	10	5.5	+52	1.98	31	..	..	..	..	..	..	..	..	..	..	..	..
24	M	42	24	..	+53	2.92	58	..	..	..	..	..	..	..	..	..	..	..	..
					Mean:	1.87 ±	30.5 ±												
						0.06	1.9												

\* Slight hemolysis.

† These patients received iodine at some time during their illness, but not for a considerable period before their treatment with thiouracil was started.

‡ This patient had received Lugol's solution for about 60 days previous to therapy, but had shown no good response.

group, with ages ranging from 20 to 35 years. Total serum magnesium varied between 1.91 and 2.68 mg. per 100 cc. with an average of  $2.28 \pm 0.03$  mg. per 100 cc. Ultrafiltrable magnesium ranged from 1.33 to 1.76 mg. per 100 cc., with a mean value of  $1.58 \pm 0.02$  mg. per 100 cc. The percentage of non-diffusible magnesium varied from 17 to 42%, with an average of  $30.4 \pm 1.1\%$ .

Table 2 shows the results obtained in 24 cases of hyperthyroidism. There were 20 females and 4 males, varying in age from 21 to 60 years. The total serum magnesium varied from 1.03 to 2.92 mg. per 100 cc., with an average of  $1.87 \pm 0.06$  mg. per 100 cc. The ultrafiltrable magnesium ranged from 0.55 to 1.90 mg. per 100 cc., with an average of  $1.28 \pm 0.03$  mg. per 100 cc. The percentage of non-diffusible magnesium varied from 5 to 58%, with an average of  $30.5 \pm 1.9\%$ .

Table 2 shows also the effect of thiouracil administration in 14 cases of hyperthyroidism. The thiouracil\* was given in daily doses of 0.6 gm. for 2 weeks, followed by daily doses of 0.4 gm. until the basal rate was approximately normal, when a maintenance dose of 0.1 to 0.2 gm. daily was given. Those patients in whom specimens were obtained after 3 weeks or more of such therapy all had undergone a remarkable clinical improvement and were gaining weight. Unfortunately, in 4 patients, levels could not be determined after 14 days of treatment because of surgical intervention or other causes.

Although the percentage of non-diffusible magnesium decreased to some extent in 6 patients (3, 5, 6, 7, 8, 10), in the remainder it was not either appreciably affected or actually rose.

TABLE 3.—A COMPARISON OF THE EFFECT OF THIOURACIL ON THE PERCENTAGE OF NON-DIFFUSIBLE (BOUND) MAGNESIUM OF SERUM AND THE BOUND IODINE OF PLASMA

Days of treatment	BMR	Bound magnesium (mg. per 100 cc.)	% of bound magnesium	Bound iodine ( $\mu$ g. per 100 cc. of plasma)
0 . . . .	+60	0.39	25	14.7
7 . . . .	+33	1.36*	40	11.4
14 . . . .	+33	1.53	22	7.2
28 . . . .	+12	1.53	35	5.6

\* Slight hemolysis.

Table 3 shows the decrease in plasma bound iodine in patient No. 2 (Table 2) while receiving thiouracil, as contrasted with the negative effect on the level of the percentage of non-diffusible magnesium.

**Comment.** Our data show the average total, diffusible, and non-diffusible serum magnesium levels of hyperthyroid patients to be slightly lower than the comparative average values for normals. The average value for the percentage of non-diffusible magnesium is almost identical in the two groups, however. The range of the percentage of bound magnesium in hyperthyroidism is strikingly varied, being just twice as great as the range for normal individuals.

It is interesting that our data differs from that of Soffer *et al.* and Dine and Laviates, not so much in the average values obtained in hyperthyroid patients, as, in the higher average percentage of bound

\* Thiouracil (Deracil) was kindly supplied by the Lederle Laboratories, Inc., Pearl River, N. Y.

magnesium found in normal individuals. Our data resembles that of Cope and Wolff more closely, although their average percentage of bound magnesium for both thyrotoxic patients and normals is somewhat higher than we obtained. The average values for the total, the ultrafiltrable, and the bound magnesium which these latter observers obtained in hyperthyroid patients are almost identical with our own. Examination of Soffer's data<sup>15</sup> shows that 22 of his 50 cases of hyperthyroidism had less than 30% of the total serum magnesium in the non-diffusible fraction, and he has recently reëmphasized the fact<sup>12</sup> that the percentage of bound magnesium is not elevated in all cases of thyrotoxicosis.

It is generally accepted that there is an excessive amount of circulating thyroid hormone in thyrotoxicosis. One of the best indices of this increase is the protein-bound iodine level of the plasma, which has been found consistently elevated in hyperthyroidism.<sup>11</sup> It has been found that thiouracil causes a decrease to normal of the basal metabolic rate and the plasma protein-bound iodine in thyrotoxicosis.<sup>18</sup> In 1 case treated with thiouracil (Table 3) in which simultaneous iodine and magnesium determinations were obtained, there was no correlation between the two levels.

The effect of thiouracil on the absolute value of non-diffusible magnesium, and the percentage of the total serum magnesium which was non-diffusible, was quite inconstant. These data would seem to suggest that magnesium probably does not represent part of the thyroid hormone *per se*. Soffer has noted<sup>13</sup> that injections of thyroglobulin into dogs causes a rise in the bound magnesium, but only after some time has elapsed. The injection of thyroxin into dogs has no appreciable effect on the magnesium fraction.<sup>14</sup> This again suggests that magnesium is probably not an integral part of the thyroid hormone.

Thyrotoxicosis causes profound alterations in most, if not all, the metabolic processes of the body. Magnesium is known to be necessary for the activity of certain enzyme and co-enzyme systems.<sup>6,9</sup> One of the best recognized of these is the pyruvate oxidation system which also requires the presence of diphosphothiamine. It is known that persons with thyrotoxicosis are deficient in diphosphothiamine, and have high pyruvic acid blood levels.<sup>20</sup> This is but one of the many metabolic alterations in thyrotoxicosis which might explain wide fluctuations in non-diffusible magnesium in this disease. The amount of protein in the diet influences the absorption of magnesium from the gastro-intestinal tract<sup>8</sup> which must also be considered in an evaluation of the magnesium partition. In view of these and many other factors which must influence such an important ion as magnesium, it appears that the magnesium partition will have to be studied in a greater number of metabolic disturbances before its significance in hyperthyroidism may be evaluated.

**Summary.** 1. Diffusible and non-diffusible serum magnesium fractions were determined in 24 hyperthyroid and 18 normal persons. In the thyrotoxic cases the non-diffusible fraction ranged between 5 and 58% of the total serum magnesium, with an average of  $30.5 \pm 1.9\%$ .

In normals the non-diffusible fraction varied from 17 to 42% of the total, with an average of  $30.4 \pm 1.1\%$ . Thus we have been unable to demonstrate significant increases in the percentage of the non-diffusible fraction of the total magnesium in hyperthyroidism.

2. Thiouracil apparently has no constant effect on the magnesium fractions in hyperthyroidism.

3. It is suggested that the variability in the magnesium fractions in thyrotoxicosis is the reflection of alterations in metabolic processes.

The author wishes to thank Dr. Robert H. Williams for valuable advice in the conduct of this study, and Dr. Roger S. Hubbard for statistical analyses of the results.

## REFERENCES

1. ASTWOOD, E. B.: J. Am. Med. Assn., 122, 78, 1943.
2. BRIGGS, A. P.: J. Biol. Chem., 52, 349, 1922.
3. CLARK, E. P., and COLLIP, J. B.: J. Biol. Chem., 63, 461, 1925.
4. COPE, C. L., and WOLFF, B.: Biochem. J., 36, 413, 1942.
5. DINE, R., and LAVIETES, P.: J. Clin. Invest., 21, 781, 1942.
6. DUCKWORTH, J.: Nutr. Abstr. and Rev., 8, 841, 1939.
7. LAVIETES, P. H.: J. Biol. Chem., 120, 267, 1937.
8. McCANCE, R. A., WIDDOWSON, E. M., and LEHMAN, H.: Biochem. J., 36, 686, 1942.
9. OCHOA, S.: The Biological Action of the Vitamins, Chicago, Univ. of Chicago Press, p. 17, 1942.
10. PHILLIPS, R. A., VAN SLYKE, D. D., DOLE, V. P., EMERSON, K., JR., HAMILTON, P. B., and ARCHIBALD, R.: Copper Sulfate Method for Measuring Specific Gravities of Whole Blood and Plasma, U. S. Navy Research Unit, at the Hospital of the Rockefeller Institute for Medical Research.
11. SALTER, W. T., and BASSETT, A. M.: Trans. Assn. Am. Phys., 56, 77, 1941.
12. SOFFER, L. J.: Personal communication.
13. SOFFER, L. J., COHN, C., GROSSMAN, E. B., JACOBS, M. D., and SOBOTKA, H.: J. Clin. Invest., 20, 429, 1941.
14. SOFFER, L. J., COHN, C., LESNICK, G., SOBOTKA, H., and JACOBS, M.: J. Clin. Invest., 23, 263, 1944.
15. SOFFER, L. J., DANTES, D. A., GROSSMAN, E. B., SOBOTKA, H., and JACOBS, M.: J. Clin. Invest., 18, 597, 1939.
16. TSCHOPP, E., and TSCHOPP, E.: Helv. Chem. Acta, 15, 793, 1932.
17. WATCHORN, E., and McCANCE, R. A.: Biochem. J., 26, 54, 1932.
18. WILLIAMS, R. H., and BISSELL, G. W.: New England J. Med., 229, 97, 1943.
19. WILLIAMS, R. H., and CLUTE, H. M.: New England J. Med., 230, 657, 1944.
20. WILLIAMS, R. H., EGANA, E., ROBINSON, P., ASPER, S. P., and DUROI, C.: Arch. Int. Med., 72, 353, 1943.

## VITAMIN LEVELS IN SPRUE\*

BY DAVID CAYER, M.D.

JULIAN M. RUFFIN, M.D.

AND

WILLIAM A. PERLZWEIG, Ph.D.

DURHAM, N. C.

(From the Departments of Medicine and Biochemistry, Duke University School of Medicine)

MOST authorities agree that sprue is due to "a profound disturbance of the power of the intestines to absorb in a normal fashion the products

\* This study was supported by a grant from the John and Mary R. Markle Foundation and the Anna H. Hanes Research Fund.

of digestion,"<sup>6</sup> and should be classified as a deficiency disease. However, the rôle of vitamin deficiencies in the production of the disease is still a controversial matter. For example, it has been reported that the glossitis of sprue will subside following the administration of nicotinic acid.<sup>7</sup> Others<sup>8</sup> have found that nicotinic acid is of no value whatever.

In the past few years, laboratory tests have been devised for the determination of the levels of various vitamins and are now fairly well standardized. By applying these laboratory methods to patients having sprue, one should be able to measure the levels or degrees of saturation of the various vitamins. This might make possible a more exact study of this disease and enable one to determine with reasonable accuracy what vitamin or vitamins are depleted in a given patient. In this communication the vitamin levels of 12 patients having sprue are reported.

**Material.** The 12 cases of sprue reported here were selected with the greatest care, on the basis of steatorrhea, glossitis, macrocytic hyperchromic anemia, flat glucose tolerance curve, and marked weight loss. Two of the patients had previously been diagnosed as having sprue, according to the criteria stated above, but were in remission at the time of this study.

For the purpose of comparison, a second group consisting of 25 patients who were diagnosed clinically as having a mild or early vitamin deficiency of the B-complex was selected. These patients were of the same economic level as that of the group having sprue and so far as could be ascertained were subsisting upon essentially the same diet. A control group of 30 normal medical students also was studied.

**Method.** The method of study was similar to that described in a previous communication.<sup>12</sup> To summarize, all patients were hospitalized and given a standard diet, low in vitamins, but adequate in proteins and calories. The control group of 30 medical students was given this diet during the period of study but allowed to continue their usual activities. The following laboratory tests for vitamins were carried out: Vitamin C was measured in the Evelyn photoelectric colorimeter, using Tillman's dye and the technique of Mindlin and Butler.<sup>9</sup> Vitamin A determinations were made by the method of Kimble.<sup>6</sup> The vitamins of the B-complex were determined in the urine before and after the following test doses: thiamin, 1 mg. i.m.; riboflavin, 5 mg. orally; nicotinic acid amide, 500 mg. orally; pyridoxine, 50 mg. orally. Thiamin was determined at first by the yeast fermentation technique of Atkin, Schultz and Frey<sup>1</sup> which includes the total thiamin and pyrimidine fractions, and later by a modification of the thiochrome method.<sup>3</sup> Riboflavin was measured by the direct fluorometric method of Ferrebee,<sup>4</sup> omitting the adsorption and elution steps. The nicotinic acid load-test was based on the previous study of Perlzweig, Sarett and Margolis.<sup>10</sup> Values for F<sub>2</sub> determined fluorometrically<sup>11</sup> paralleled closely those for total nicotinic acid excretion. Pyridoxine was determined colorimetrically by the technique of Scudi *et al.*,<sup>13</sup> including the form hydrolyzed by heating with acid.

**Results.** The vitamin levels in the 3 groups, as determined by the procedures described above, were compared and are shown in the accompanying tables and charts. The "suggested lower limit of normal" as shown in the accompanying charts was based upon a previously reported study.<sup>2</sup>



*Vitamin A.* The plasma levels of vitamin A in the 30 normal students show a distribution and a mean well above those of the 25 patients having vitamin deficiencies (Chart I). It is important to

TABLE 1.—ARITHMETICAL MEANS OF VITAMIN LEVELS

Vitamins	30 Student controls	25 B complex deficiencies	12 Sprue	Suggested lower limit of normal
A . . . . .	115.0	89	48	.75
Carotene . . . . .	265.0	205	49	165
C . . . . .	0.67	0.33	0.06	0.15
Nicotinic acid . . . . .	88	48	57	65
Thiamin: Control period . . . . .	672	455	260	400
Load-test . . . . .	415	150	156	300
Riboflavin: Control period . . . . .	810	490	280	400
Load-test . . . . .	3300	2100	1630	2200
Pyridoxine . . . . .	7.0	5.2	5.8	4.7

Vitamin A—international units per 100 cc. of plasma.

Carotene—international units per 100 cc. of plasma.

Vitamin C—mg. per 100 cc. of plasma.

Nicotinic acid—urinary excretion in mg. in 14 hrs. after test dose of 500 mg. orally.

Thiamin: Control period—urinary excretion in gamma in 24 hrs.

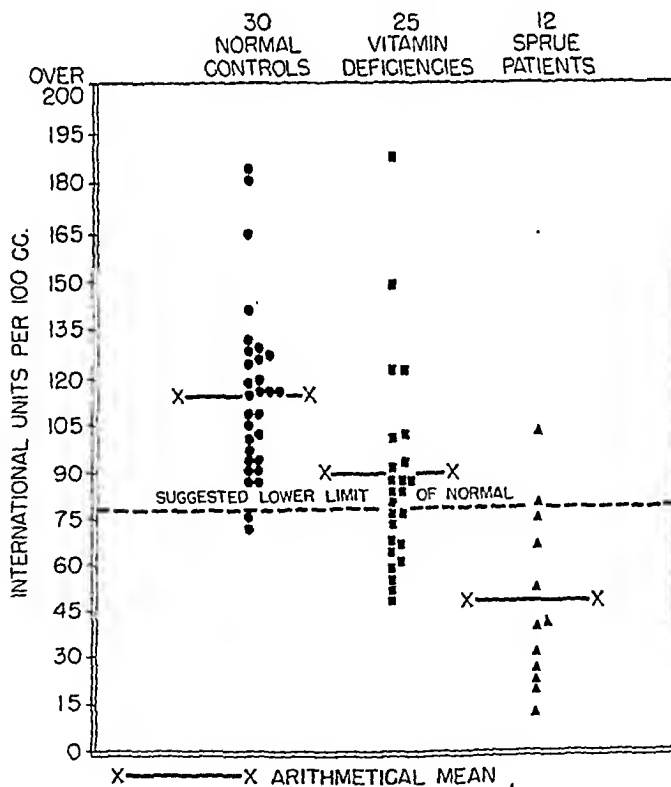
Load test—urinary excretion in gamma in 4 hrs. after 1 mg. intramuscularly.

Riboflavin: Control period—urinary excretion in gamma in 24 hrs.

Load test—urinary excretion in gamma in 24 hrs. after 5 mg. orally.

Pyridoxine—urinary excretion in mg. in 4 hrs. after 50 mg. orally.

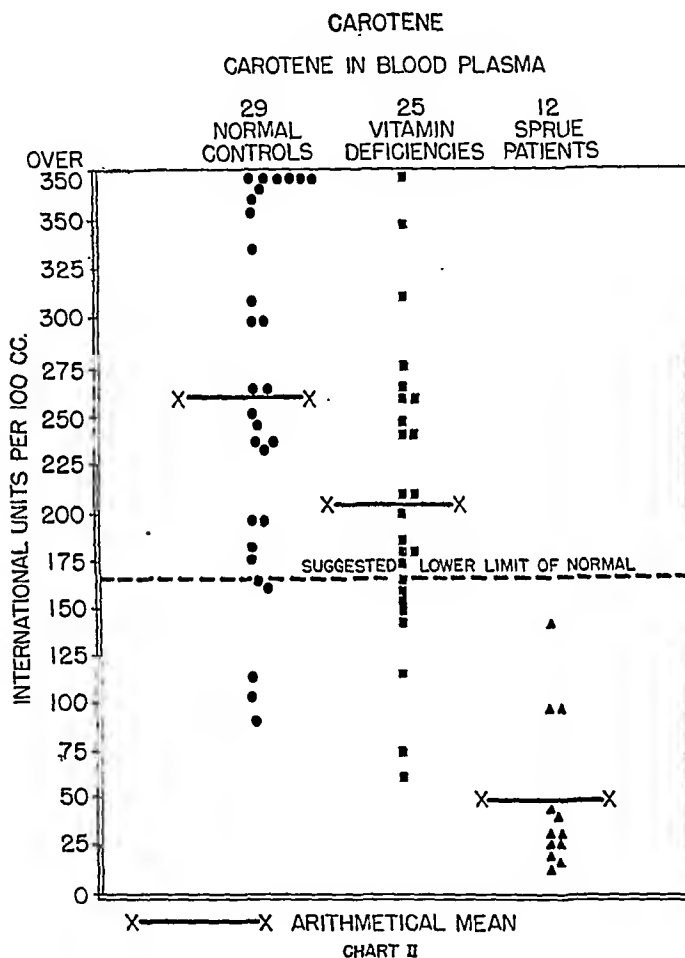
VITAMIN A  
LEVELS OF VITAMIN A IN BLOOD PLASMA



X ——— X ARITHMETICAL MEAN ,  
CHART I

note that the values in the 12 patients having sprue were likewise much lower than those of the deficiency group (Table 1). Nothing to suggest a vitamin A deficiency clinically was observed in any of these patients.

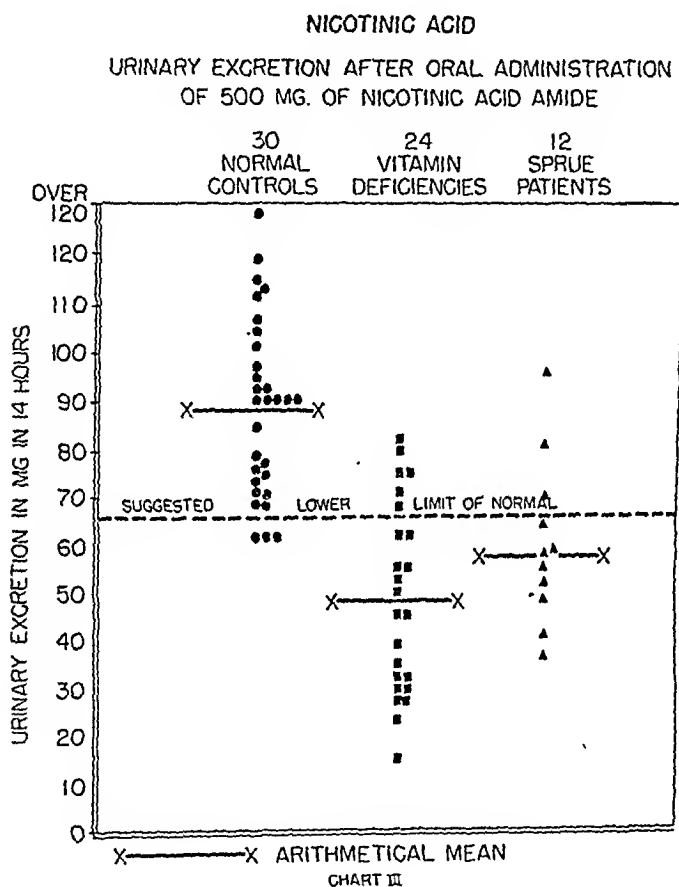
*Carotene.* The general distribution of values for plasma carotene between the three groups was the same as that in vitamin A, yet the difference between the mean in those patients having sprue and those of the other groups is even more marked (Chart II).



*Vitamin C.* While there were individuals in each group whose plasma contained no measurable vitamin C, still over half of the patients having sprue had levels of zero, and the remainder were below 0.3 mg. per 100 cc. (Table 1). None of the patients showed any clinical evidence of scurvy.

*Nicotinic Acid.* A comparison of the urinary excretion of nicotinic acid in the three groups, following the administration of 500 mg., is of interest. It will be noted that the mean of the patients having sprue is somewhat higher than that of the deficiency group, but both were considerably lower than the normal controls (Chart III).

*Riboflavin.* The distribution of values of the urinary excretion of riboflavin, both during the control period and after the oral administration of 5 mg. in the 3 groups, is shown in Charts IV and V. The mean of the patients having sprue was definitely lower than that of the patients classified as having a vitamin deficiency and both were significantly lower than that of the normal control group.

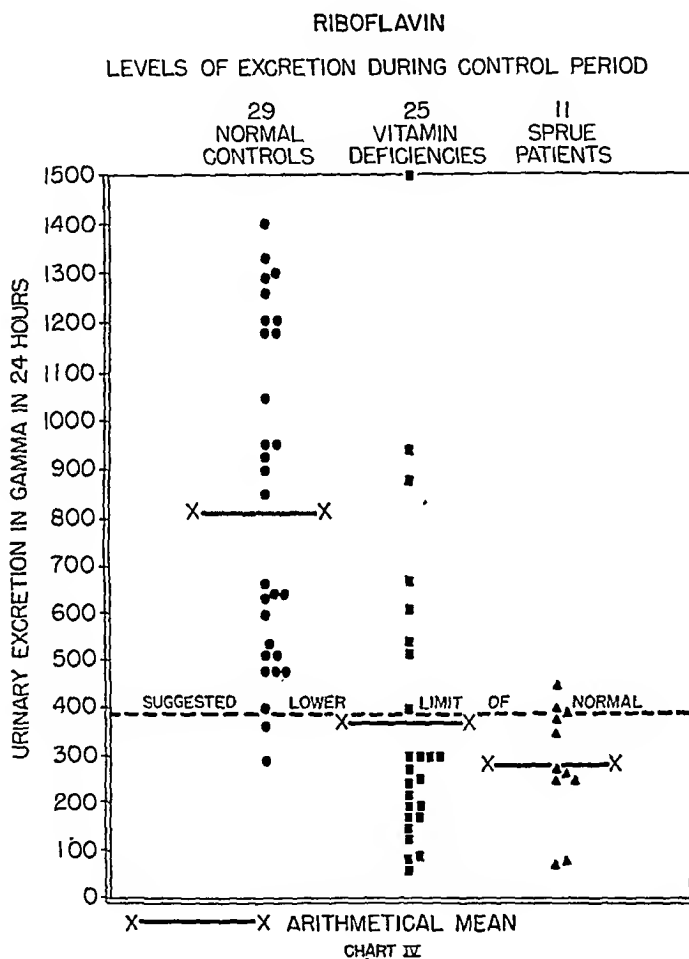


*Thiamin.* During the control period of thiamin excretion, the distribution of values between groups was essentially the same as in riboflavin. However, after the intramuscular administration of 1 mg. of thiamin, the means of the excretion levels were the same in those patients having sprue as in those having a vitamin deficiency, although both were well below that of the normal control group (Table 1).

*Pyridoxine.* There were no significant differences in distribution or mean values of the 3 groups in the urinary excretion of pyridoxine, after the oral administration of 50 mg. (Table 1).

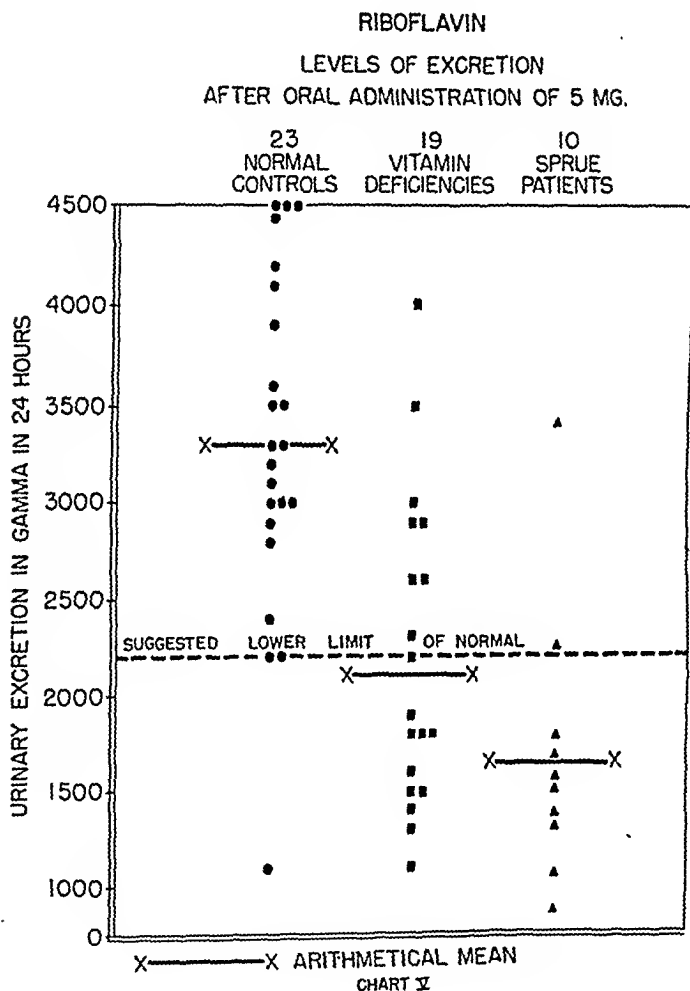
**Discussion.** It is generally recognized that single deficiencies are rarely if ever seen clinically. In sprue with the anorexia which regularly accompanies the disease, the diarrhea and interference with intestinal absorption, one would naturally expect multiple vitamin deficiencies to be present. The findings in this study confirm this

impression. One notes that patients with sprue are apt to have low values for the B-complex and vitamin C. This is especially true of thiamin and riboflavin. However, the nicotinic acid levels in the patients with sprue were a little above those of the 24 patients classified clinically as having a vitamin deficiency. A possible explanation of this finding might lie in the fact that in sprue there is marked wasting with destruction of body tissues, and this would afford a certain amount of nicotinic acid for utilization by the body.



The striking difference, however, between the sprue patients and the patients having clinically a B-complex deficiency is in the vitamin A and carotene levels. Here we see that the plasma level of vitamin A is much lower than in the deficiency group and that the depletion of carotene in the blood plasma is even more striking. This is to be expected, since it is known that fats are poorly absorbed in sprue, and vitamin A and carotene being fat-soluble are lost as a result. It might be suggested that the diarrhea alone is responsible for these low levels. However, a comparison with patients having amebic dysentery shows that such is not the case. The mean of the plasma

vitamin A in 8 patients having amebic dysentery was found to be 91 international units, which is within normal limits, and almost twice that of the sprue patients, which was found to be 50 I.U. The same marked difference is noted in the carotene levels. In the 8 patients having amebic dysentery the mean was 141 I.U. as compared with a mean of 50 I.U. in the sprue group. This would suggest that carotene is absorbed chiefly in the small intestine. Likewise there is a striking difference between the carotene and vitamin A levels in sprue as compared



with those in pernicious anemia. In 8 patients having pernicious anemia, the mean for vitamin A was found to be 83 I.U. and that of carotene 154 I.U. as compared with a mean of 50 I.U. in both vitamin A and carotene in the sprue group. The determinations of plasma vitamin A and carotene are relatively simple procedures and can be carried out in any well-equipped laboratory. The striking differences in the distribution and means of vitamin A and carotene suggest that these determinations may prove helpful not only as an aid in the diagnosis of sprue, but also in distinguishing it from pernicious anemia.

**Conclusions.** 1. Multiple deficiencies of the B-complex are the rule in patients having sprue.

2. The plasma levels of vitamin A and carotene in patients having sprue are significantly lower than the levels of normal individuals, as well as those of patients who have clinical evidence of a B-complex deficiency.

3. The determination of the plasma levels of vitamin A and of carotene is a useful laboratory procedure in the recognition of sprue.

#### REFERENCES

1. ATKIN, L., SCHULTZ, A. S., and FREY, C. N.: *J. Biol. Chem.*, **129**, 471, 1939.
2. CAYER, DAVID, RUFFIN, J. M., and PERLZWEIG, W. A.: *South. Med. Jour.*, (in press).
3. EMMETT, A. D., PEACOCK, C., and BROWN, R. A.: *J. Biol. Chem.*, **135**, 131, 1940.
4. FERREBEE, J. W.: *J. Clin. Invest.*, **19**, 251, 1940.
5. HANES, F. M.: *Tice Practice of Medicine*, W. F. Prior Co., **4**, 171, 1944.
6. KIMBLE, M. S.: *J. Lab. and Clin. Med.*, **24**, 1055, 1939.
7. MANSON-BAHR, P.: *Lancet*, **2**, 317, 1940.
8. MAY, C. D. *et al.*: *J. Pediat.*, **21**, 289, 1942.
9. MINDLIN, R. L., and BUTLER, A. M.: *J. Biol. Chem.*, **122**, 673, 1938.
10. PERLZWEIG, W. A., SARETT, H. P., and MARGOLIS, L. H.: *J. Am. Med. Assn.*, **118**, 28, 1942.
11. NAJJAR, V. A., and WOOD, R. W.: *Proc. Soc. Exp. Biol. and Med.*, **44**, 386, 1940.
12. RUFFIN, J. M., CAYER, DAVID, and PERLZWEIG, W. A.: *J. Gastroenterol.*, (in press).
13. SCUDY, J. V., BUHS, R. P., and HOOD, D. B.: *J. Biol. Chem.*, **142**, 323, 1942.

## EARLY FILARIASIS (BANCROFTI) IN AMERICAN SOLDIERS\*

BY CAPT. IAN G. HODGE, M.C., A.U.S.

CHIEF OF THE UROLOGICAL SECTION

CAPT. ERIC DENHOFF, M.C., A.U.S.

CHIEF OF THE LABORATORY SERVICE

AND

LT. COL. JOSEPH B. VANDER VEER, M.C., A.U.S.

CHIEF OF THE MEDICAL SERVICE, HQ. 364TH STATION HOSPITAL, UNIT 1, A.P.O. 322  
SAN FRANCISCO, CALIF.

FILARIASIS (bancrofti) is a widespread disease occurring in tropical and subtropical countries of both the eastern and western hemispheres. It is prevalent in the Pacific Islands, southern Asia, Africa, the West Indies, and along the northern coast of South America.

Our present concept of the disease begins with the discovery of microfilariae in the hydrocele fluid of a resident of Cuba by Demarquay (see Belding<sup>2</sup>) in 1863. In 1866, Wucherer recovered microfilariae from chylous urine and 10 years later Bancroft isolated an adult worm from a lymphatic associated with a filarial lesion of the arm. In 1878, Manson described the life cycle of the filaria with the mosquito acting as the intermediate host.<sup>13</sup> In more recent years, extensive studies have been made by Bahr,<sup>1</sup> O'Connor,<sup>10</sup> and Buxton<sup>3</sup> of the disease as it occurs in the Pacific islands. The early manifestations of filariasis,

\* We regret the delay in publication of this article, which apparently left the hands of the authors last July and reached ours in March.—EDITOR.

as seen in the Armed Forces of the United States, have been described recently by Dickson *et al.*<sup>4</sup>

**The Life Cycle of *Wuchereria Bancrofti*.** *Wuchereria bancrofti* is a species of nematode (Order—Spirurida; Sub-order—Spirurina; Superfamily—Filarioidea; Family—Dipetalonematidea; Genus—*Wuchereria*).

Man is the only known definitive host. Microfilariae circulate freely in the peripheral blood of certain infected persons. The intermediate host is a mosquito\* which aspirates the microfilariae† while sucking blood from an infected person. Metamorphosis takes place in the mosquito, being completed in a minimum of 8 to 9 days. During this time the larvæ have burrowed through the intestinal wall to the thoracic muscles, then to the proboscis where they are in the infective stage and from which they escape to a new definitive host. The mature larvæ break out of the tip of one or the other of the two labellæ which form the end of the labium.<sup>7</sup> They are probably incapable of penetrating normal skin but enter the subcutaneous tissues through the wound left by the mosquito. They enter the lymphatic where they mature into adult sexual forms. The maturation period takes from 3 to 12 months. The production of microfilariae requires the fertilization of an adult female by an adult male. The microfilariae thus produced enter the blood stream either by way of the thoracic duct or by penetrating the lymph spaces and entering the small vessels in the vicinity.

**Clinical Syndrome.** This series to be reported consists of 62 cases in which a diagnosis of filariasis bancrofti‡ was made. (Many more cases have been seen with symptoms and physical signs suggestive of such a diagnosis, but these cases are not included in the series.) All the patients reported were exposed to filariasis for 364 days.

The clinical cases may be divided into 5 groups (Table 1). The number and anatomic location of the lesions is shown in Charts 1 and 2. One or more case histories will be presented to demonstrate each group. Complete histories, and physical examinations were done but only the significant findings will be recorded. In the early cases demonstrating genital involvement, elaborate confidential questionnaires were prepared and repeated urine specimens and prostatic smears were examined to rule out venereal infection.

**Case Abstracts.** CASE 1. Age 22. Eight months after leaving an island in the South Pacific, this patient noticed discomfort in his left testicle. This gradually became more severe and radiated up the left spermatic cord to the left groin. On the morning of the 3rd day after first noticing the pain, the left

\* Although *Culex quinquefasciatus* (*Culex fatigans*) and *Aedes scutellaris pseudoscutellaris* (*Aedes variegatus*) are probably the most important, metamorphosis has been observed in at least 41 species of mosquitoes, including *Anopheles* and *Mansonia*.

† Investigators\* have found that 3 microfilariae per c.mm. will produce optimal infestation, that 0.5 will fail to infect, and that 10 will kill the mosquito. Bachman found that 84% of 565 *Culex fatigans* were infected with an average of 4 larvæ following a blood meal with a concentration of 1.75 microfilariae per c.mm.

‡ It is assumed that the parasite concerned was *Wuchereria bancrofti*. The appearance of the microfilariae and the fact that this species is endemic on the island where the troops were stationed substantiated this view.

"testicle" became swollen and the patient was admitted to the hospital. Examination of the genitalia revealed a definite thickening of the spermatic cord and a nodular, tender enlargement of the epididymis on the left side. The right and left inguinal and the left axillary lymph nodes were enlarged. On the 3rd day following admission, a hydrocele of moderate size was present. This gradually subsided. On the 4th day, there was edema of the scrotum. A painful and tender red streak was also visible in the left abdominal wall extending diagonally from the costal margin to a point just below and lateral to the umbilicus. The lymphangitis disappeared in 2 days but the scrotal edema persisted for 5 days. During his illness, this patient complained of pain radiating down the mesial aspect of the upper third of both thighs.

TABLE 1.—CLINICAL CLASSIFICATION OF EARLY FILARIASIS

Group	Clinical manifestations	No. of cases
I	Cases characterized by genital manifestations	47
II	Cases characterized by superficial lymphangitis of the extremities	13
III	Cases characterized by multiple lesions	16*
IV	Cases suggestive of involvement of the deep lymphatics	1†
V	Asymptomatic cases with microfilariae in the blood	1
Total:		62

\* Not included in the total. When multiple lesions occurred, the first to appear is recorded in the group classification.

† This case is referred to elsewhere as "doubtful" but is included in the series to complete the clinical classification.



CHART 1.—Number of patients in each clinical group.

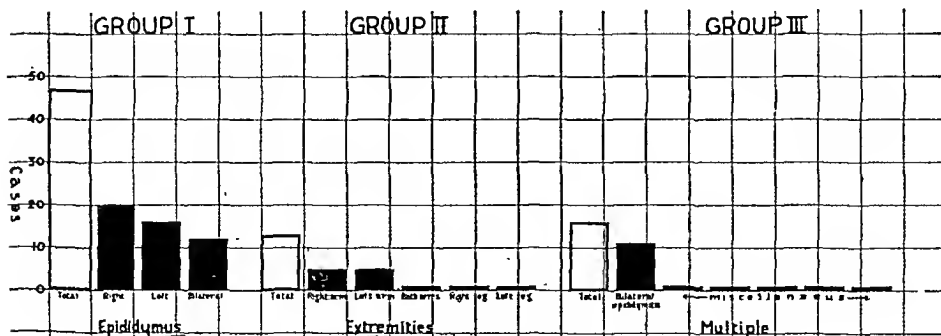


CHART 2.—Anatomic location of lesions by clinical groups.

At the time of evacuation from the combat zone 29 days after admission, slight thickening of the spermatic cord and epididymis was still present.



*Laboratory Studies.* Repeated urinalyses were negative; differential leukocyte count showed 6% eosinophils; venous blood concentrated and examined for microfilariae was negative.

This case demonstrates the typical, mild genital involvement classified in Group I. In addition, it is the only case presented demonstrating multiple lesions (Group III).

CASE 2. Age 27. Four months after leaving the endemic area this soldier developed a pain in the left lower quadrant of the abdomen following heavy manual labor. During the night the pain radiated down the spermatic cord to the testicle. The next morning, swelling of the left "testicle" was noticed. Examination showed tenderness, and thickening of the left spermatic cord and epididymis. A small hydrocele was noticed. One large left inguinal lymph node was palpable. The pain continued. The hydrocele increased in size and was aspirated on the 3rd day for the relief of symptoms. After the 7th day, the pain subsided. The genital swelling decreased slowly until when last seen only slight thickening of the spermatic cord and epididymis remained.

*Laboratory Studies.* Repeated urinalyses were negative; differential leukocyte counts showed 7% eosinophils. Examination of the fluid aspirated from the hydrocele showed no microfilariae. A microfilaria was found at 10:30 P.M. on the 3rd day of hospitalization, in the peripheral blood (cover-slip technique). Repeated examinations throughout 24-hour periods thereafter failed to demonstrate microfilariae. This is the only case of the symptomatic cases showing microfilaria in the blood. The genital manifestations are typical of Group I.

CASE 3.—Age 25. Two months after leaving the endemic area, this soldier developed a pain in the mesial aspect of the right arm. He was admitted to the surgical service of the hospital with a diagnosis of acute lymphangitis—cause undetermined. No abrasion or infection could be found to account for the lesion. The right axillary lymph nodes were large and tender. Within a week the patient was well. Six months later, the patient became aware of a painful and tender "lump" in the right axilla. The following day, pain radiated from the "lump" down the mesial aspect of the arm and within 24 hours a red streak was visible from the axilla to the midpoint of the antero-mesial aspect of the arm. The patient was admitted to the hospital. On the 3rd day from the onset of the symptoms, examination revealed a diffuse swelling of the mesial aspect of the right arm. A red streak was visible. On palpation, a firm "cord" could be felt underlying the streak. There was increased local heat. The axillary lymph nodes were enlarged and tender. Three distinct nodes could be palpated. The patient could put his finger on the particular node which gave rise to his first symptom. The epitrochlear lymph nodes were palpable on both sides. Two days after admission, the right axillary lymph node indicated by the patient as the source of his pain was removed for biopsy. A live adult filaria was found in the node.

During the next week, the lymphangitis progressed distally to the wrist. By this time the signs previously present in the upper arm had disappeared except that the thickened lymphatic was still palpable. The patient was evacuated from the combat zone 17 days after admission.

*Laboratory Studies.* Repeated urinalyses were negative; differential leukocyte count showed 4% eosinophils. Repeated examinations of the capillary and venous blood failed to show microfilariae.

This case is typical of Group II, but is the only one in which an adult filaria was recovered.

CASE 4. Age 23. Seven months after leaving the endemic area, this patient developed a dull aching pain in the right side of the abdomen associated with occasional twinges of pain in the right testicle. The pain gradually subsided. Three weeks later he developed severe pains in the right flank which radiated down to the anterior aspect of the right thigh. The pain was aggravated by rising from the supine to the sitting position. An aching pain radiated down the mesial aspect of both thighs when the patient walked short distances. Examination revealed tenderness below the right costovertebral

angle which extended laterally to the crest of the ileum. The entire right side of the abdomen was tender to deep pressure. There was questionable thickening of the right spermatic cord. Roentgen ray of the abdomen and lumbar spine was negative.

*Laboratory Studies.* Repeated urinalyses were negative; differential leukocyte count showed 4% eosinophils; no microfilariae were found in the peripheral blood on repeated examinations.

This case is representative of a considerable number of "doubtful" cases suggestive of deep lymphatic involvement, referred to in Group IV. It is included to complete the clinical classification.

CASE 5.—Age 25. Five months after leaving the endemic area, this soldier developed a slight transient pain in the left testicle. Examinations by one of us at that time revealed a small varicocele on the left side. The wearing of a suspensory was advised and the pain was relieved. Three months later, microfilariae were found in the peripheral blood during a survey of asymptomatic patients exposed to filariasis. Specific questioning revealed that for the past 3 days the soldier had noted a transient needle-like pain in the right testicle but it was so slight that he disregarded it. Examination of the genitalia was negative except for a varicocele on the left side. The right and left inguinal, the left axillary and the left epitrochlear lymph nodes were enlarged. The patient was hospitalized for observation. That night he noticed a dull aching pain in his right testicle, and the following afternoon it radiated up the spermatic cord to the right lower quadrant of the abdomen. Three days later he complained of a similar symptom in the left side. At this time the physical findings were not impressive but there was slight thickening of both spermatic cords. The pain in the right side disappeared promptly but persisted on the left side. Ten days later, definite thickening and induration of the left spermatic cord and epididymis could be demonstrated. The manifestations gradually subsided.

*Laboratory Studies.* Repeated urinalyses were negative; repeated differential leukocyte counts showed a mean eosinophilia of 7%. The results of smears taken for microfilaria are indicated in Table 2.

TABLE 2.—RESULTS OF EXAMINATION FOR MICROFILARIAE IN CASE 5

1st day:	10 A.M. (survey)—9 microfilariae per drop (cover glass technique)
	12 NOON—no microfilaria (conc. specimen)
	1 P.M.—no microfilaria (conc. specimen)
	3 P.M.—no microfilaria (conc. specimen)
	6 P.M.—no microfilaria (conc. specimen)
	9 P.M.—1 microfilaria per drop (conc. specimen)
	11 P.M.—no microfilaria (conc. specimen)
2nd day:	13 conc. specimens examined; all negative
3rd-6th days:	3 conc. specimens examined; all negative
7th-28th days:	1 conc. specimen examined; negative

This case represents Group V because at the time microfilariae were found the patient had not complained of any discomfort and showed no positive physical manifestations.

*Laboratory Studies.* MATERIAL. On 50 of the 62 clinical cases presented, laboratory studies were fairly complete. These included complete blood counts, frequent differential leukocyte counts, examinations of the blood, aspirated fluids and urine for microfilariae. Histopathologic and bacteriologic studies were performed on several lymph nodes. Bacteriologic studies were also made on aspirated fluids, blood and urine. Feces were examined for intestinal parasites and ova, the urine for chyluria. Skin tests were made on some patients. Examinations of the blood for microfilariae and differential leukocyte counts were also made on 142 asymptomatic soldiers who were exposed to filariasis.

METHODS. 1. *Examination for Microfilariae.* The technique found to be most satisfactory in searching for microfilariae will be described in detail:

(a) Unconcentrated preparations are made by placing a drop of blood on a cover-slip; another cover-slip is superimposed and pressed gently until the blood is spread evenly on both slips. These are pulled apart quickly and placed blood down on a glass slide. They are examined as "wet" preparations under the low power objective. A moderately thin preparation will facilitate the finding of microfilariae.

(b) Concentrated "wet" preparations are made by mixing 20 cc. of venous blood in a solution consisting of 100 cc. of 5% formalin, 5 cc. of 2% glacial acetic acid, and 1 cc. of 1% safranin. This is centrifuged for 2 hours. The supernatant fluid is removed and the residue examined as in (a). When a large number of specimens are to be examined, it is more convenient to concentrate only 2 cc. of blood in 10.5 cc. of fluid. These preparations keep well for several weeks.

(c) Stained thick smears are prepared by spreading a large drop of blood on a glass slide. The smears are dried for several hours and then laked in 0.01% saponin solution for 20 minutes. These are stained with diluted Wright's stain (1 cc. diluted with 45 cc. distilled water) for 1 hour. The smears are not washed or blotted. Concentrated sediment from urine and aspirated fluids are examined in the same way.

2. *Examination for Adult Filariae.* A search was made for adult filariae by gross, microscopic and roentgenographic examinations of lymph nodes and lymph vessels. The lymph nodes were either sectioned and gently teased apart under a hand lens, or were bisected and placed in normal saline solution at 40° C. Histopathologic sections of these nodes were examined. Roentgenograms for the detection of calcified adult filariae were made in several instances.

3. *Skin Tests.* The technique of skin testing will be considered under the discussion of skin tests.

**Positive Diagnostic Laboratory Observations.** 1. *Microfilariae.* Of 266 soldiers examined, only 2 were found with microfilariae. Actually this represented over 2000 preparations examined at various periods during the day and night. Both were found on unconcentrated "cover-slip" preparations. Identification was made under the low power objective. On a "wet" preparation, the microfilariae varied from 80 to 300  $\mu$  in length and 8 to 12  $\mu$  in width. They were gracefully curved, had bluntly rounded ends anteriorly, while the posterior third of the body tapered to a point. In 1 instance, an oscillating motion was observed within the sheath. This was not observed in others, although in some there was a sluggish bending motion of the posterior third of the body for a short time. On high power magnification several uniform, round, evenly spaced nuclei dispersed through the anterior three-fourths of the body were observed. Staining by Wright's stain was weak and only the nuclei were clearly defined.

2. *Adult filariae.* Eight lymph nodes were examined for adult filariae. In only 1 instance was a worm found. It was obtained by placing a bisected lymph node in normal saline solution at 40° C.; the live worm appeared on the cut surface of the gland. It was creamy white and smooth in appearance. Under the low power objective it was found to be curled on itself several times. It was estimated to be 30 mm. in length and 0.1 mm. in width. A bluntly rounded anterior end and a simple cylindrical esophagus could be identified.

**Other Laboratory Observations.** 1. *Hematologic Studies.* Red blood cell counts and hemoglobin were within normal limits. The average

leukocyte count was 6000 to 8000. The differential leukocyte counts were within normal limits except for eosinophils. An eosinophilia of 9% or more was considered abnormal.

In a survey of 509 soldiers studied at the hospital during a period of 8 months, all of whom had been stationed in the tropics 16 months or more, it was found that 269 (Group A) had been exposed\* to filariasis and 240 (Group B) had been stationed on filarial-free islands. In Group A, 50 (18.5%) were found to have eosinophilia; in Group B, only 13 cases (5.4%) had this finding (Table 3). Group A was divided into Sub-group *a*—those with manifestations of filariasis, and Sub-group *b*—those who had no manifestations of filariasis. Analysis revealed that 33 (24.2%) of 136 soldiers constituting Sub-group *a* had eosinophilia, while 17 (12.7%) of 133 patients in Sub-group *b* had this finding. The per cent eosinophilia varied from 9 to 36% (Table 4). Sub-group *a* was further divided into Sub-group *a*-1, those with clinical filariasis, and Sub-group *a*-2, those with minimal or doubtful manifestations of the disease. Seven (14%) of the 50 cases constituting Sub-group *a*-1 had eosinophilia, whereas 26 (30.2%) of the 86 cases in Sub-group *a*-2 had this finding (Table 5). Chart 3 correlates graphically the findings outlined in Tables 3, 4 and 5.

TABLE 3.—THE INCIDENCE OF EOSINOPHILIA IN SOLDIERS STATIONED IN THE TROPICS 16 MONTHS OR MORE

Group	No.	Cases with eosinophilia (9% or above)	eosinophilia (%)
A. Exposed to filariasis . . .	269	50	18.5
B. Not exposed to filariasis . . .	240	13	5.4

TABLE 4.—THE INCIDENCE OF EOSINOPHILIA IN SOLDIERS EXPOSED TO FILARIASIS

Sub-group	No.	Eosinophilia	
		Cases	%
A. Soldiers with manifestations of filariasis . . .	136	33	24.2
B. Soldiers without manifestations of filariasis . . .	133	17	12.7

TABLE 5.—THE INCIDENCE OF EOSINOPHILIA IN SOLDIERS WITH FILARIASIS

Sub-group	No.	Eosinophilia	
		Cases	%
<i>a</i> -1. With clinical filariasis . . . . .	50	7	14.0
<i>a</i> -2. With minimal or doubtful filariasis . . . . .	86	26	30.2

The above data suggest: the incidence of eosinophilia (9% or above) is significantly greater in soldiers exposed to filariasis as compared to those living in the tropics but not exposed to the disease. In exposed troops with manifestations of filariasis, the incidence of eosinophilia is greater than in those with no evidence of the disease. It is of interest that the incidence of eosinophilia in those with minimal or questionable filariasis was twice as great as in those with frank clinical manifestations of the disease.

\* "Exposure" in this study implies continued residence in an endemic filarial area for 365 days.

2. *Histopathologic Examinations.* Eight lymph nodes and 2 hypertrophied lymphvessels removed from patients with filariasis were examined histologically. Some will be described in detail:

(a) **PATIENT A.** Patient noticed a painful swelling of his right arm which receded promptly. The right axillary and epitrochlear lymph nodes were enlarged. Differential leukocyte count revealed 3% eosinophils.

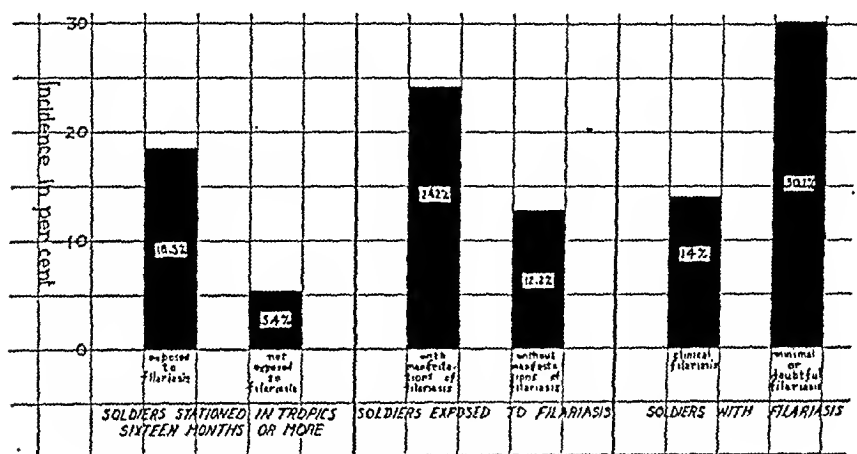


CHART 3.—The incidence of eosinophilia (9% or more).

The lymph node vessel removed for examination revealed an irregular mass of fibro-fatty tissue 0.8 x 0.5 x 0.3 cm. in size. Serial microscopic section showed multiple focal areas of necrosis were present. Some of these areas were hyalinized, filled with degenerating cellular debris and surrounded by neutrophils. The reticulum and lymph channels contained many eosinophils and neutrophils. The lymph vessel showed inflammatory thickening of the walls. *Impression:* acute focal lymphadenitis.

(b) **PATIENT B.** A few months prior to admission to the hospital the patient noticed enlarged left axillary lymph nodes. He was admitted because of pain and a swelling on the mesial side of his left arm. Within 2 days, redness, heat and swelling of the entire mesial aspect of the left arm and forearm were present. A red nodular palpable lymphatic extended from the axilla down the mesial side of the arm and across the antecubital fossa. The left epitrochlear lymph node was readily palpable. Differential leukocyte count revealed 8% eosinophils. After the acute process had subsided, the left epitrochlear lymph node and a portion of the lymphatic vessel were removed.

Gross examination revealed a discrete lymph node 1 x 0.5 x 0.4 cm. in size. The cut surface was grayish white and cellular in appearance. The lymphatic vessel was a thin fibro-fatty cord 6 cm. in length and 0.3 x 0.5 cm. in diameter along which were many small oval firm nodules. Histologic sections of the node revealed acute and subacute inflammatory changes, characterized by focal hyaline necrosis and diffuse eosinophilic infiltration through the reticulum. Neutrophilic infiltration, especially in the "pale centers," in some places was quite dense. There was edema, eosinophilic, plasma cell, and lymphocytic infiltration of the pericapsule. The lymphatic vessel showed inflammatory reaction and early fibroblastic proliferation. The attached lymph nodes were undergoing the same changes as the epitrochlear node. In addition, areas of early fibroblastic proliferation were present in these glands as well as the periglandular connective tissue. *Impression:* subacute lymphadenitis.

(c) **PATIENT C.** (Refer to Case 1.) A lymph node from the left inguinal region was removed for biopsy. Gross examination revealed a lymph node 1.5 x 1 x 0.5 cm. in size. The cut surface was grayish white and cellular.

Microscopic sections showed an inflammatory reaction characterized by diffuse infiltration of the reticulum with eosinophils which in some areas appeared in dense clumps. In other places the lymph sinuses contained many neutrophils. The lymphoid follicles and germinal centers were large and hyperplastic. The pericapsular connective tissue was edematous, infiltrated with many eosinophils and plasma cells and showed early fibrosis. *Impression:* subacute lymphadenitis with benign lymphoid hyperplasia.

(d) PATIENT D. This patient developed a painful swelling of the right epididymis and spermatic cord 3 months after leaving the endemic area. A firm nodule was palpable in the thickened spermatic cord about 2 inches proximal to the epididymis. The differential leukocyte count revealed 4% eosinophils. The nodule was removed for study.

Gross examination of the specimen revealed a lymph node 4 cm. in diameter. The cut section revealed a hard, slightly raised area measuring 4 mm. in length and 2 mm. in width. Roentgenograms of this node demonstrated a "comma-shaped" area of calcification. A broad zone of inflammatory reaction consisting mainly of epithelioid cells and Langhans giant cells surrounded the necrotic tissue. There was marked eosinophilic infiltration. Scarring, round cell infiltration, and increased vascularity were present at the periphery. A few dilated endothelial lined spaces, probably lymphatics, were seen. *Impression:* chronic granuloma with necrosis and calcification.

(e) PATIENT E. This patient was admitted to the hospital because of large, tender axillary lymph nodes on the right side. One node was removed for biopsy. At the same time a punch biopsy was taken from a right inguinal node. Four days later he developed acute centrifugal lymphangitis of the right arm which was associated with the development of a large discrete tender axillary node on the affected side.

Gross examination revealed a lymph node 1.2 x 0.8 x 0.5 cm. in size. The cut surface was pale and cellular. Microscopic examination was marked by infiltration of the reticulum and lymph sinuses with eosinophils, plasma cells and polymorphonuclear leukocytes. Focal areas of necrosis were present. The stroma was very vascular. There were isolated areas of fibroblastic proliferation and for the most part the lymphoid follicles were large and hyperplastic. *Impression:* subacute lymphadenitis with benign lymphoid hyperplasia.

Other investigators have had greater success in finding adult filaria in biopsied lymph nodes. Dickson<sup>6</sup> found filariæ in 6 of 14 lymphatic tissues from Marines with clinical filariasis. O'Connor<sup>11</sup> has stressed the eosinophilic infiltration and early fibroblastic proliferation seen in enlarged lymph node of patients with filariasis. This is not dependent on the presence of an adult filaria in the node but is probably allergic in nature.

Our findings are comparable to this description. Eosinophilic infiltration was the most constant finding. The additional findings of fibroblastic proliferation, focal necrosis and hyalinization further suggest that the changes are due to an allergin rather than a bacterial infection.

3. *Skin Tests.* In early cases of filariasis because microfilariae are seldom found in the blood and the demonstration of adult filariæ is also difficult, the development of a satisfactory cutaneous test would be of great aid in the diagnosis of this disease. Fairley<sup>5</sup> has reported favorably on an intracutaneous test made from an extract of dog heart worm, *Dirofilaria immitis*, which is closely related to *W. bancrofti*. Mohr and Lippelt<sup>9</sup> have shown this test may also be positive in the presence of other nematodes. A complement-fixation test using an

extract of *Contortospiculum rheæ*, a filaria found in South America, may be more specific for filariasis. They report a small percentage of false positives. Dickson,<sup>4</sup> using an extract of the *D. immitis*, reports over 80% positive intracutaneous tests in patients with early filariasis and 4.7% positive tests in patients who have lived for several months in areas where filariasis is endemic. They described a positive test as one characterized by an immediate wheal reaching a diameter of 15 mm. or more, and by an edematous reaction occurring within 24 hours, measuring at least 20 mm. in diameter. Delayed reactions were recorded as doubtful.

As we were unable to obtain an extract of the *Dirofilaria*, an antigen\* was made from an epitrochlear lymph node removed from a patient with filariasis manifested by superficial lymphangitis of the arm and who had an eosinophilia of 17%. No adult filaria was found in the node. The rationale for this was the possibility that allergy may play an important rôle in filariasis. It is reasonable to postulate that the allergen from the adult filaria may be present in sufficient concentrations in enlarged lymph nodes so that patients sensitive to a common allergin would react. Lippelt and Mohr<sup>5</sup> have shown that in Ascariasis, the antigen was derived from the products of metabolism of the worm, rather than from the worm itself. If this is true in filariasis, this test could be valuable, provided there is sufficient concentrations of "metabolic substances" in affected lymph nodes. The lymph node was digested with 0.6% pepsin in 0.3% hydrochloric acid at 37° C. for 12 hours. It was strained and diluted with an equal amount of normal saline solution and permitted to stand until the supernatant fluid was clear. This was removed and the residue treated with acetone and ether until a powder was obtained. It was preserved in a sufficient amount of 0.4% phenol in normal saline solution to make a 1:20 dilution. Eleven patients with clinical filariasis and 15 patients not exposed to the disease were tested by injecting 0.1 cc. of the solution intracutaneously. A control consisting only of menstruum was injected simultaneously. The test was considered positive when an erythematous wheal at least 0.5 cm. in diameter appeared within 36 hours. These positive reactions resembled a weakly positive Schick test. Of 11 patients with clinical filariasis, 7 (64%) showed positive reactions varying from 0.5 to 2 cm. in diameter. All controls were negative. There was no relation of the degree of eosinophilia to the intensity of the reaction. The intracutaneous reactions could in no way be compared to the reaction attributed to the extract of *D. immitis*. Because adult filariæ were not found in the gland, this experiment cannot be regarded as a specific test. However, it suggests that these patients were more or less sensitive to a common allergin present in an enlarged lymph node from a patient with early filariasis.

4. *Other Pertinent Data.* Repeated urine examinations for chyluria were done in all cases. Feces were examined to eliminate intestinal parasites as a cause for eosinophilia. Other common causes for

\* This antigen was prepared by the method described by Sawitz for making *Trichinella* antigen.<sup>1</sup>

eosinophilia were excluded. Bacteriologic studies were done on biopsied lymph nodes and on aspirated fluid from lymph nodes, hydroceles, and a prepatellar bursa. Blood cultures and urine cultures were done on several patients. Pathogens were not obtained in any instance. The aspirated fluids were examined for microfilariae but none were observed.

**Discussion.** It is to be kept in mind that this paper deals only with the early manifestations of filariasis. These lesions are due in some way to the presence of adult filariae.

The manner in which adult filariae produce the clinical manifestations is uncertain, but the following hypotheses deserve consideration: (1) Mechanical obstruction of lymphatics. (2) An allergic response to the living or dead adult filariae or their products. (3) The discharge of microfilariae by the fertilized adult female. (4) Secondary infection.

Bahr, Buxton and others have observed that microfilariae disappear from the blood during an attack of acute lymphangitis. This has been demonstrated in clinical Case 5 of our series. If obstruction plays a part in this phenomenon, it follows that the adult filaria causing the obstruction is the one producing microfilariae at that time. Although this may be the case in early or minimal infestation, it seems unlikely in advanced cases. Some of the lymph nodes and both of the lymph vessels which we removed for study showed fibroblastic proliferation and the lymph vessels were greatly thickened. This proliferative response to filariae has been observed by Lane,<sup>2</sup> and could readily be a factor in obstruction. In addition the retrograde nature of the lesions suggest that there is some lymph stasis in the involved vessel. Contrary to the theory of obstruction, is the fact that in practically all parts of the body lymphatic anastomosis is very rich.

There is considerable evidence that allergy plays an important rôle. The very nature of the superficial lesions suggests an allergic response. The blotchy redness of the skin and the lack of severe constitutional manifestations in the presence of an acute inflammatory reaction are characteristic of allergy. The eosinophilic response as observed in the peripheral blood and the biopsied specimens is strong evidence in support of this theory. The allergin may be present in the living adult worms or be a product of their metabolism. The fact that many investigators, including ourselves, have found living worms in lymph nodes proximal to the affected parts, substantiates this. In contrast to this, O'Connor has shown that there is a more marked reaction around dead than living filariae. The allergin may be produced by the disintegration of dead worms. No dead worms were found in this study. A high per cent of soldiers exposed to filariasis had eosinophilia. It is difficult to attribute their allergic response to dead filariae because eosinophilia was observed also in those without manifestations. Eosinophilia was not present in all our clinical cases. The eosinophilic response to an allergin varies with the individual. In no disease in which eosinophilia is a characteristic response, would one expect to find it in every case.

That the acute manifestations of filariasis are not due to the sudden



release of large numbers of microfilariae from the blood during acute attacks, and the fact that microfilariae may be present in large numbers in the peripheral blood without causing symptoms, is sufficient evidence to cast grave doubt on such a theory.

The theory that the acute manifestations are caused by secondary bacterial infections is supported by the work of Grace,<sup>6</sup> who was successful in isolating beta-hemolytic streptococci in pure culture from the blood stream and the local lesions. The bacteriologic studies which we carried out, although incomplete, failed to demonstrate the presence of pathogenic organisms. It should be pointed out that the work of Grace and others regarding secondary infection has been done on natives, in whom the filarial infestation could be regarded as in a "late" stage. In such advanced cases, especially those with elephantoid lesions, secondary infection probably does play a part. Our studies suggest that the lymphangitis of early filariasis is an allergic response to a protein present in an adult filaria or a product of its metabolism. The response is manifest along a lymphatic which has been damaged or partially obstructed by adult filariae or by the reaction to them.

The native term "mumu" is used extensively in the South Pacific Islands to describe both the acute lymphangitis described by Grace and the lymphangitis seen in early cases. The term is an ambiguous one that does not differentiate the bacterial from the bacteria-free lesions. The early lesions of filariasis are best demonstrated as they occur in clinical Group II. These lesions are superficial; the lymphatics are visible and drain into lymph nodes that are generally accessible for biopsy.

The manifestations depend on the location of the particular lymph node in which the adult filaria responsible for the reaction is located. Thus if the adult filaria is located in certain pelvic or peri-aortic lymph nodes, the genital manifestations of Group I result. If the worm is in a lymph node draining the superficial lymphatics of the extremities, the manifestations will be those of Group II. Similarly if the lymph node affected is one draining a deep lymph vessel where the reaction cannot be seen or felt, the diagnosis is not evident as in Group IV. The important fact is that the clinical manifestations will depend on the site of the node in which the adult filariae causing the manifestations are located.

The clinical manifestations seen in Clinical Groups I and II are so typical and constant that the diagnosis on a clinical basis is seldom in doubt. The diagnostic criteria are outlined as follows:

a. *Involvement of the Genitalia.* 1. It frequently follows manual labor.

2. Testicular pain is the most common complaint.

3. The pain may radiate up the spermatic cord or may first appear in the lower quadrant of the abdomen and radiate down the spermatic cord to the testicle.\*

\* In 1 of our patients, right lower quadrant pain was present for 1 month before more definite manifestations were evident. A cigar-shaped tumor caused by the enlarged spermatic cord as it traversed the inguinal canal was seen the day prior to epididymal involvement. This demonstrates the centrifugal nature of the lesion.

4. The spermatic cord and epididymis are thickened and indurated.
5. An acute hydrocele is frequently present during the early stages.
6. Pain in the upper mesial aspect of the thigh on the affected side may be present.

7. Scrotal edema may also be present.

The most constant physical sign is the edema of the spermatic cord without involvement of the vas deferens. In the acute stages of the disease it is sometimes difficult to identify the structures of the cord on digital examination, but as the inflammation subsides, one is always able to demonstrate that the involvement does not affect the vas deferens.

*b. Involvement of the Superficial Lymphatics of the Extremities.* 1. Pain in the extremity radiating distally is the principal complaint. This pain may first be noticed in the proximal lymph nodes.

2. The extremity affected soon becomes edematous.

3. A definite "red streak" characteristic of acute lymphangitis appears proximally. The affected lymphatic is palpable, and generally only a single vessel is involved.

4. There is increased local heat.

5. The lesion extends centrifugally.

6. Resolution begins proximally and also extends centrifugally.

7. The lymph glands draining the affected part are enlarged and tender.

8. Severe constitutional manifestations are absent.

9. There is no evidence of a focus of infection distally. In Group IV, the manifestations follow no definite pattern. In the majority of cases, as in Case 4, the diagnosis is presumptive. In any patient exposed to filariasis, one must be constantly on the alert for manifestations suggesting deep lymphatic involvement. By and large we have felt that the diagnosis of involvement of the retroperitoneal lymph nodes has been easier to recognize clinically than involvement of the deep lymphatics of the extremities. Pain in the flank or the abdomen, with radiation to the genitalia or the thigh is the principal complaint. Examination reveals tenderness of the abdomen on the affected side both anteriorly and posteriorly. In such cases it is necessary to rule out renal or ureteral disease which these findings may simulate. The only complaint in patients thought to have involvement of the deep lymphatics of the extremities is pain, with peripheral radiation. Slight swelling may or may not be present. The differential diagnosis includes skeletal, muscular and neurologic conditions. These are extremely difficult to rule out and in only few instances have we felt that this has been done to our entire satisfaction.

The absolute laboratory proof of filarial infestation depends upon the finding of either adult or microfilariae. The difficulty of finding microfilariae in these early cases cannot be overemphasized. Of 251 clinical cases reported by Dickson, in none were microfilariae found. We were more fortunate in finding them in 2 instances (Cases 1 and 5).\*

\* The fact that only 1 microfilaria was observed in Case 1 left some doubt as to the significance of this finding. In Case 5, however, microfilariae were observed on 2 occasions in appreciable numbers.

In order to find an appreciable number of microfilariae in the peripheral blood, the total number present in the circulating blood must be enormous. When this occurs, it is probable that the microfilariae are being produced by more than 1 adult female. We can assume that the degree of filarial infestation in our cases is slight because of the relatively short period of exposure compared to residents of endemic areas. Therefore, because the number of adults is dependent on the number of larvæ transmitted by the mosquito\* and because the production of microfilariae is further dependent on the fertilization of an adult female, the chances of microfilariae being produced in these early mild cases are not great. Also, as the microfilariae may disappear with the onset of clinical manifestations, the chances of finding them in the early clinical cases are lessened.

The finding of adult filariae in lymph nodes has also been difficult in our cases. The lymphangitis of early filariasis characterized by centrifugal progression must be due to the presence of an adult filaria in a lymph node at the proximal end of the involved lymphatic. In clinical cases, where the involved lymph node is accessible for biopsy, it is imperative to select the correct node if one is to find filariae. We believe that most of our biopsies were poorly selected. This probably accounts for the low incidence of adult worms recovered by us. In Case 3, the selection of the correct node for biopsy was obvious because the patient could put his finger on the axillary "lump" which caused his earliest symptom. In the remainder of the lymph nodes taken for biopsy (described under laboratory studies) a review of the histories and physical findings, suggests that in each case the node selected for biopsy was not the ideal one from which to recover filariae. Although the recovery of adult filariae is impractical where the involvement is deep, if one is careful in the selection of the lymph node for biopsy where the involvement is superficial, adult filariae should be found in a high percentage of cases. The histopathologic findings in the lymph nodes and vessels removed by us had in common areas of subacute inflammation with eosinophilic infiltration and did not resemble the acute lymphadenitis caused by bacteria. This is a general eosinophilic response to an allergic process.

The incidence of eosinophilia as shown in Table 3 leaves little doubt that the soldiers exposed to filariasis had a significantly greater incidence of eosinophilia than those not exposed. This difference in the 2 groups is of even greater significance because over one-half of the soldiers in Group B (those not exposed to filariasis) were found to have systemic disease commonly associated with eosinophilia (euthanasic diseases, helminthiasis and so forth).

The breakdown of Group A (soldiers exposed to filariasis) into subgroups as shown in Tables 4 and 5 requires amplification. The 136 patients in Sub-group *a* include the patients seen with definite clinical

\* The mortality of larvæ from the time they are deposited on the skin until they reach the lymphatics is great. The larvæ are lymphotactic. Lymph exuded at the site of the mosquito bite transmits the larvæ through the wound to the lymph spaces. Such a transmission is dependent on ideal conditions.

filariasis and also many others who had what is referred to in Subgroup *a-2* as minimal or doubtful filariasis. The latter includes patients with such non-conclusive manifestations as vague testicular pain, history of recent previous swellings, vague pains in the extremities with or without swelling, slight thickening of the spermatic cord, small hydroceles, and generalized unexplained lymphadenopathy. Because these findings alone were inconclusive, the high incidence of eosinophilia assumes significance. As shown in Table 5, this subgroup had the highest incidence of eosinophilia. This finding may represent a greater allergic response during the earliest clinical stages of the disease. Subsequent observations on these patients after evacuations to a General Hospital<sup>14</sup> revealed that many of these patients developed typical clinical filariasis. In addition, skin tests done at this base, using an antigen made from *Dirofilaria immitis*, were positive in a majority of those exposed.

**Epidemiology.** The soldiers we observed were all exposed to filariasis for 364 days. Typical clinical manifestations of the disease were seen in over 11% of those exposed. It is difficult to estimate the probable rate of infestation. New clinical and doubtful cases are still appearing, even though the troops have been away from the endemic area for 8 months. It is not unlikely that the rate of infection is well in excess of 50%. Thus in endemic areas even though the period of exposure is relatively short, there is considerable danger of acquiring the disease. In our clinical cases, the percentage with microfilariae is very small. As far as we know, no other investigators have reported the recovery of microfilariae from such cases. It is conceivable, however, that many of these cases prior to the onset of clinical manifestations have had microfilariae in their blood. Further observations are necessary to exclude the possibility of microfilariae appearing at a later date.

**Prognosis.** The prognosis of these early mild filarial infestations cannot be definitely stated at this time. The local lesions are dependent on the number and location of adult filariae. It is probable that only a small percentage of the adults present cause manifestations. The lymphangitis, although frequently recurrent, does not leave any demonstrable permanent damage as far as we have observed.

The end-result of extensive filarial infestations may be elephantiasis. However, even in the natives of endemic areas, the percentage that develop elephantiasis is very small. There is good evidence that such late manifestations are due to a secondary bacterial infection superimposed on a damaged lymphatic system.

In these early cases, therefore, when the exposure to filarial infestations has been relatively short and the damage to the lymphatic system minimal, the prognosis appears to be good. The adult filariae present in the body may live for a number of years, but eventually die and become organized.

Psychosomatic manifestations have been reported by Rome and Fogel.<sup>12</sup> This was not a serious problem in the cases we observed. In retrospect, it is thought that this may have been avoided by individu-

ally reassuring those hospitalized and by instruction of all exposed troops by the commanding officer and the battalion surgeon. Emphasis was placed on the fact that no serious complication or permanent damage was likely to occur as a result of minimal filarial infection.

**Prophylaxis and Treatment.** Spread of the disease by early cases must be considered. Further observation is necessary to determine the extent of this problem. Until such time as more data are available, all soldiers with a history of exposure to the disease in an endemic area should be considered possible carriers.

Any troops going into filarial areas should have the advantage of specialized mosquito control. In addition, protection of the individual by the use of mosquito bars, head nets, leggings, long shirt sleeves, sprays and repellents is of great importance. Native villages should be "off limits" to all troops and natives prohibited from entering bivouac areas. Camp sites should be chosen as far removed from native villages as is practical.

Treatment of early filariasis consists of supportive measures. The lesions appear to be self-limited. During the acute stage, the patient should be hospitalized and the affected part put at rest. Mild analgesics are generally sufficient to control the discomfort. In some of our first cases the sulfonamide drugs were used but no change in the course of the disease was observed. Psychotherapy is essential in those patients who show undue concern regarding the final outcome of the disease. This has frequently been engendered by having seen natives with elephantiasis and by rumors of impotence and sterility.

Prevention of reinfection is an important aspect of treatment. Those with clinical manifestations and others similarly exposed should be observed in filaria-free areas with adequate mosquito control.

**Summary and Conclusion.** 1. A clinical diagnosis of early filariasis (bancrofti) has been made on 11% of a group of soldiers exposed to *Wuchereria bancrofti* on an island in the South Pacific for a period of 364 days.

2. The criteria on which a clinical diagnosis of early filariasis can be made has been outlined.

3. The diagnosis has been proved by the finding of adult and microfilariae.

4. A clinical classification has been presented, based on the anatomic location of the lesion.

5. A high incidence of eosinophilia occurred. Eosinophilic infiltration and fibroblastic proliferation has also been noted in histopathologic studies.

6. We believe that the early manifestations are due to an allergin present in, or produced by, living adult filariae and manifest along a lymphatic obstructed by the presence of, or the reaction to, the filariae.

7. The clinical diagnosis is not dependent upon the finding of adult filariae or microfilariae.

8. Clinical manifestations may be multiple and are subject to recurrences.

9. The prognosis must be guarded but in the light of our present knowledge, it appears to be favorable if reinfection is prevented.

10. The clinical cases responded well to supportive therapy.

11. Some of the early cases may be carriers and rigid mosquito control should be carried out until more is known regarding the status of these patients.

We are indebted to Dr. G. A. M. Heydon, School of Tropical Medicine, University of Sydney, and to Col. Henry M. Thomas, Jr., M.C., A.U.S., for their suggestions; to Capt. Emmett B. Settle, M.C., A.U.S., for histopathologic examinations; to T/3 Richard Nobbe, T/3 Bernard Piper, and Cpl. Charles Crow and others in the laboratory service for their many hours of work beyond the call of duty.

#### REFERENCES

1. BAHR, P. H.: Filariasis and Elephantiasis in Fiji, Monograph, London, 1912.
2. BELDING, D. C.: Textbook of Clinical Parasitology, New York, Appleton-Century, Chap. XXI, 1942.
3. BUXTON, P. H.: Researches in Polynesia and Melanesia, Monograph (Parts 5-7), London, November, 1928.
4. DICKSON, J. G., HUNTINGTON, J. R., and EICHOLD, S.: Filariasis in Defence Force, Samoan Group, Prelim. Rep., U. S. Naval Bull., 41, 5, 1943.
5. FAIRLEY, N. H.: Skin Test and Complement-fixation Test in Filariasis, Trans. Roy. Soc. Trop. Med. Hyg., 24, 220, 1932.
6. GRACE, A. W.: Tropical Lymphangitis and Abscesses, J. Am. Med. Assn., 123, 8, 1943.
7. HEYDON, G. A. M.: Personal communication.
8. LIPPELT, H., and MOHR, W.: The Diagnosis of Filariasis, Klin. Wchnschr., 17, 1684, 1938.
9. MOHR, W., and LIPPELT, H.: Report on Further Results With Filaria Complement Fixation Reaction, Klin. Wchnschr., 19, 157, 1940.
10. O'CONNOR, F. W.: Researches in the Pacific, Monograph, London, 1923.
11. O'CONNOR, F. W.: Etiology of Disease Syndrome in *Wuchereria bancrofti* Infections, Trans. Roy. Soc. Trop. Med. Hyg., 26, 12, 1932.
12. ROME, H. P., and FOGEL, H.: The Psychosomatic Manifestations of Filariasis, J. Am. Med. Assn., 123, 15, 1943.
13. STRONG, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, 6th ed., Philadelphia, Blakiston, Chap. 46, 1942.
14. THOMAS, HENRY M., JR.: Personal communication.

### TULAREMIC PNEUMONIA

#### REVIEW OF AMERICAN LITERATURE AND REPORT OF 15 ADDITIONAL CASES

BY BYRON M. STUART, M.D.

ASSISTANT IN MEDICINE, TULANE UNIVERSITY OF LOUISIANA SCHOOL OF MEDICINE AND  
CHARITY HOSPITAL OF LOUISIANA AT NEW ORLEANS

AND

ROSCOE L. PULLEN, M.D.

INSTRUCTOR IN MEDICINE, TULANE UNIVERSITY OF LOUISIANA SCHOOL OF MEDICINE;  
ASSISTANT DIRECTOR, CHARITY HOSPITAL OF LOUISIANA AT NEW ORLEANS  
NEW ORLEANS, LA.

(From the Department of Medicine, Tulane University of Louisiana School of Medicine  
and Charity Hospital of Louisiana at New Orleans)

THE marked increase in the number of reported cases of tularemic pneumonia in the past several years<sup>11,23,37,47</sup> indicates clearly that such frequent pulmonary involvement is additional evidence of the general-

ized, systemic nature of tularemic infections. In 1941, Blackford and Casey<sup>41</sup> found 150 reported cases of tularemic pneumonia in the American literature and added 12 additional cases of their own. Up to September 1944, we were able to collect 253 cases of tularemic pneumonia from the American literature. We propose herein to summarize the observations of 21 cases of tularemic pneumonia observed in the Charity Hospital of Louisiana at New Orleans. Six of these cases have been previously reported,<sup>47,66</sup> thus we are reporting 15 additional cases, bringing the total of collected cases of tularemic pneumonia in the American literature up to 268.

The first published reference to pleuropulmonary tularemia was apparently that reported by Verbrycke<sup>65</sup> in 1924, when he described in a patient dying of tularemia a number of nodules in the lungs, which were the size of hickory nuts and had the appearance of metastatic carcinoma, accompanied by a pleural effusion of 100 cc. Whitish nodules on the pleura and distributed throughout the lungs were observed in 1928 by Bardon and Berdez.<sup>4</sup> During the same year, Francis<sup>25</sup> called attention to the frequency of bronchopneumonia as a terminal event in cases of tularemia, and Simpson<sup>66</sup> suggested that the physical signs of consolidation in such cases might well be due to areas of caseous necrosis resulting from tularemia rather than to other types of bronchopneumonia. Likewise in 1928, Bunker and Smith<sup>15</sup> first recovered *Bacterium tularense* (*Pasteurella tularensis*) from the sputum. Massee,<sup>43</sup> in 1931, described a case of confluent pneumonia in which *B. tularense* was isolated. Permar and MacLachlan,<sup>48</sup> in the same year, described generalized areas of consolidation of a necrotic type which they called tularemic pneumonia. They expressed the opinion that necrosis had been produced by the extreme interstitial edema with monocytic infiltration and subsequent stenosis and thrombosis of the smaller veins and arteries. Also during 1931, Sante<sup>55</sup> described the roentgenographic findings of pleuropulmonary tularemia. Subsequent reports<sup>3,5,9,10,12-14,16,19-22,24,28-31,33,34,41,46,49,51,53,59,61,64,67,68</sup> of pleuropulmonary tularemia have been increasingly frequent.

**Pathogenesis.** That *B. tularense*, the organism which causes tularemia, is transmissible to man from animals has been well established.<sup>57</sup> Of the 268 cases of tularemic pneumonia available for study in the American literature (including 15 cases of our own), a definite history of contact with animals was available in 115 cases and may be summarized as follows: rabbits in 92 instances, ticks in 13, squirrels in 3, deerflies in 2, and woodchuck, opossum, cat, chicken hawk, and rat each in 1 case. In 2 additional cases, the probable source of infection was laboratory exposure in 1 instance and performance of an autopsy in another.

It is interesting to note that only 171 of the 268 patients (63.8%) had ulceroglandular, oculoglandular, or glandular types of the disease, whereas 97 cases (36.2%) had no demonstrable primary lesions or lymphadenopathy and may be classified, therefore, as the typhoidal type of infection. Foshay<sup>23</sup> observed that 52.2% of 46 typhoidal cases had pneumonia, while approximately 15% of 554 cases of other

types of tularemia developed evidences of pneumonia. Kavanaugh<sup>37</sup> found that 12.7% of his series of 123 patients had pneumonia. Similar figures were reported also by Blackford and Casey,<sup>11</sup> and Bihss and Berland.<sup>6</sup> It would appear, therefore, that pneumonia occurs most frequently in those cases without evidences of lymphadenopathy or primary lesions. Some appreciation concerning the incidence of typhoidal tularemia may be derived from the observation of Francis<sup>26</sup> to the effect that typhoidal tularemia represented 6.4% of 1856 collected cases.

Two schools of thought have sought to explain the mechanism by which *B. tularensis* reaches the lungs: hematogenous dissemination and inhalation. Kavanaugh<sup>37</sup> and Simpson<sup>56</sup> favor the hematogenous point of view, as does the evidence submitted by Foshay<sup>23</sup> that there are two blood stream invasions, an initial one and a second bacteremia 5 or 6 days preceding death in many of the fatal cases. Permar and MacLachlan,<sup>48</sup> on the other hand, have suggested direct infection of the respiratory tract through inhalation and have discussed representative cases in which cutaneous ulceration and regional adenopathy were lacking. Bunker and Smith,<sup>15</sup> and others<sup>32,47</sup> have successfully recovered *B. tularensis* from the sputum of patients with tularemic pneumonia. Recently, Aagaard<sup>1</sup> has reported the case of a graduate student in bacteriology who contracted tularemic pneumonia after an infected rabbit sneezed in the student's face. Several other laboratory workers have developed tularemia without presenting evidences of ulceration or regional adenopathy.<sup>57</sup> In 7 of 16 cases of Kavanaugh's series,<sup>37</sup> the infection appeared to originate as a primary pneumonia, suggesting that infection entered *via* the respiratory tract.

Comparative analysis of tularemia with other infections favors the inhalational method of infection. The similarities of tularemia to tuberculosis have been pointed out by Blackford,<sup>7</sup> while McCoy<sup>45</sup> referred to tularemia in animals as a "plague-like disease of rodents." Bihss and Berland<sup>6</sup> have recently discussed the clinical similarities between tularemic and bubonic plague. Reimann<sup>53</sup> states that the pathogenesis of primary pulmonic tularemia, like that of plague, is apparently inhalational in mode, such as inhaling bacilli suspended in the air as dust, in droplets from patients or animals who have tularemic pneumonia, or from handling dried cultures of the organisms.

Blackford and Casey<sup>11</sup> believe that infection through inhalation is rare if it does occur, and that failure to find the portal of entry does not mean that the organism entered *via* the respiratory tract. Eight of our 21 cases had no demonstrable portal of entry or evidences of regional lymphadenopathy. Historical data pertaining to these cases were, however, insufficient in most instances to determine whether or not inhalation of the organisms should be considered as the route of infection.

**Morbid Anatomy.** Blackford and Casey<sup>11</sup> found 56 necropsy reports of tularemia in the literature, but apparently overlooked Matthews' pathologic findings<sup>44</sup> of 3 patients who died from tularemic infection. Of the 56 autopsy records collected by Blackford and Casey,<sup>11</sup> lesions



of tularemic pneumonia were described in 35 cases, an incidence of 62.5% in fatal cases. Since Blackford and Casey's survey of the American literature, 39 additional necropsy reports<sup>2,6,17,18,27,36,38,40,44,47,60,62,63,66,69</sup> have appeared and lesions of tularemic pneumonia were described in 34 of these reports. It is evident, therefore, that of 95 patients who died of tularemia and who were subjected to post-mortem examination, 69 presented lesions of tularemic pneumonia, an incidence of 72.6% in fatal cases.

Both the gross and the histologic features of tularemic pneumonia and tularemic pleural effusions have been discussed in detail by Lillie and Francis.<sup>42</sup> Recently, Blackford and Casey<sup>11</sup> reviewed the pathologic changes of pleuropulmonary tularemia and concluded that additional records of autopsies served only to verify previous observations. Although pneumonic involvement of the lungs is more frequent and more serious, an accompanying pleural reaction may be seen in about 50% of the cases of tularemic pneumonia. Thus, of 32 collected cases which proceeded to autopsy, Lillie and Francis<sup>42</sup> found pleural exudates in 16 cases and focal nodular lesions in the pleura in one other instance.

The most frequent pulmonic involvement in fatal cases is a lobular or confluent lobular form of pneumonia which may involve a single lobe, several, or all of the lobes. In cases with all the lobes involved, some lobes may contain only discrete nodules. It is not infrequent at postmortem examination to find lesions in all of the lobes. The usual phases of both gray and red hepatization are frequently found. The areas of gray hepatization present regions of central whitish or yellowish necrosis, which, on cut surface, not infrequently reveal small or large areas of coagulation or caseous necrosis and occasionally small, scattered, interseptal areas of focal necrosis. In some cases,<sup>8</sup> cavitation is present and may resemble those of chronic pulmonary tuberculosis. Pneumothorax, presumably resulting from a ruptured abscess, has been described.<sup>37</sup>

On microscopic examination, it will be found that the exudate is most frequently composed of mononuclear cells which are often phagocytic in character. A few lymphocytes, red cells, desquamated epithelial cells and plasma cells may be present. When secondary infection with the various cocci is superimposed, many neutrophils may be found in addition to the above reaction. The alveolar spaces are filled with a similar exudate which may contain fibrin at times. The alveolar septa are usually congested, especially in the pneumonic areas, and frequently the walls are necrotic. Interstitial infiltration by lymphocytes, mononuclear cells and other cells is not marked and is often confined to the interlobar septa, peribronchial and perivascular tissues. Some of the blood-vessels show mononuclear infiltration, necrosis and thrombosis.<sup>48</sup> The perivascular lymphatics may be distended with a cellular or caseous exudate. Lillie and Francis<sup>42</sup> found that the areas of focal necrosis in the lung apparently were simply necrosing pneumonic foci. According to some reports,<sup>43</sup> *B. tularensis* have been seen in the lesions, but are rarely isolated or cultured from the pulmonic lesions as a general rule.

**Symptoms.** The symptoms presented by patients with tularemic pneumonia usually fall into two general groups: In the first group, the pneumonia is associated with the ulceroglandular, glandular, or oculoglandular types of tularemic infection and may occur from 1 or 2 days to many months after the localized infection elsewhere has developed. Thus, the symptoms of the pneumonia may occur with or follow the symptoms of tularemia elsewhere in the body, although the symptoms of pneumonia usually predominate in either case. In the second group, evidence of ulceration and lymphadenopathy is lacking. In these cases of typhoidal or cryptogenetic type of tularemia, the infection frequently appears to originate as a primary pneumonia, suggesting, therefore, that the infection may have entered through the respiratory tract. In this group, the onset may be sudden with a chill, fever, dyspnea, cough, pain in the chest and profuse sweating. The cough may or may not be productive. These patients appear extremely ill and are frequently suspected of having typhoid fever.

The pulmonary symptoms may vary greatly in severity. Frequently the symptoms are so mild that, without roentgenographic evidence, pneumonia cannot be recognized. In general, the pulmonary symptoms may be said to be less severe in character than those associated with other primary forms of pneumonia. Symptoms of bronchitis are usually present before pneumonia is recognized. Blackford and Casey<sup>11</sup> found cough present in 19 of 20 cases. Sputum was produced in only 50% of their patients; this varied in amount and occasionally was blood-tinged. Pleuritic or chest pain was experienced by 11 patients. Six patients were dyspneic.

The fever curve of tularemic pneumonia is usually irregular and spiking in nature, while the pulse rate is usually relatively slow in comparison, except for the tachycardia observed in the more severe or terminal cases. Rapid and shallow respirations, cyanosis, delirium, confusion or stupor, with rapid progress to a comatose state, may be observed in the most severe cases and, according to Foshay,<sup>23</sup> is frequently associated with a recurrent or secondary bacteremia.

**Physical Findings.** The physical signs of tularemic pneumonia vary with the type and distribution of lesions. Both lungs are frequently involved. In general, the physical findings are those of an atypical pneumonia. The patchy areas of consolidation are usually indicated by irregularly distributed and more or less circumscribed areas over which râles, bronchovesicular or bronchial breathing, and increased whispering pectoriloquy may be heard. These findings may vary in location and intensity from day to day. Occasionally, a lobar type of pneumonic consolidation may be demonstrated. Rarely, abscess cavities may be suspected in an occasional protracted case by the presence of amphoric breath sounds and "cracked-pot" resonance during percussion.

Physical examination of the chest may reveal no abnormal findings in some patients even though pleuropulmonary involvement can be demonstrated roentgenographically. Hence, roentgenographic studies of the chest of any patient with tularemia are advisable, since pulmo-

nary involvement in the form of an atypical pneumonia, with or without areas of focal necrosis, pleural effusion, nodular infiltration and peribronchial thickening is often found in the absence of significant physical findings.

**Roentgenographic Diagnosis.** In their patients with pleuropulmonary tularemia, Bihss and Berland<sup>6</sup> found that the most consistent Roentgen findings in the chest were enlarged and nodular hilar shadows, which usually occurred early in the disease. Frequently, these hilar shadows are not recognized as important until later accentuation of the lung markings radiating to the periphery have developed.

Bihss and Berland consider two basic types of pleuropulmonary involvement in tularemia. Non-typhoidal cases are thought to present usually hilar adenopathy in the early stages of the disease with subsequent retrograde extension through lymphatic channels into the lung parenchyma or even into the pleura with production of a pleural effusion. The second basic type is found in cases of typhoidal tularemia where the lung parenchyma is thought to be involved primarily and is usually not preceded by hilar adenopathy. The consolidations are large, homogeneous, and satisfy the roentgenographic criteria of pneumonia.

Abscess cavities are occasionally demonstrated roentgenographically in cases of pulmonic tularemia. Blackford and Casey<sup>11</sup> observed pneumothorax in 1 case and lobar atelectasis in another instance. Residual changes such as increased fibrosis are found in many cases.

Figures 1 to 4 show roentgenograms of the chests of 4 of our patients and have been selected to demonstrate the variety of roentgenographic findings seen.

**Diagnosis.** In typical cases of tularemia, the diagnosis of an accompanying pneumonia is not difficult if careful observations of the individual patient are made for evidences of pulmonic involvement, such as an increase in pulse rate, respiratory rate, fever, and the appearance of cough and sputum. Confirmation of the diagnosis should be made by roentgenographic studies. It is not possible, however, to be certain whether the pulmonary lesion is tularemic in nature or caused by a secondary infection with the wide variety of organisms normally present in the upper respiratory tract unless *B. tularensis* can be demonstrated by bacteriologic methods.

In the typhoidal forms of tularemia, not only the pulmonic involvement must be demonstrated but the etiology of the underlying febrile state must be suspected and determined. In that connection the diagnosis of tularemia should be entertained in prolonged fevers of undetermined etiology. Moss and Weilbaecher<sup>47</sup> have reviewed the recent advances in the diagnosis of tularemia and have concluded that the diagnosis of a small percentage of cases, in which an occupational history, primary lesion, ulceration and lymphadenopathy are lacking, rests entirely upon the laboratory data, including the blood culture, agglutination tests, and animal inoculations. In their opinion, the blood culture is not generally reliable. Agglutination tests, especially if there is a rising titer, are of more value, but cannot be relied upon

until after the second week of the disease, and in fulminating infections may be delayed or may actually never develop throughout the entire course of the disease. Material secured by lung puncture or aspirated from the lymph nodes, blood and sputum may be inoculated into small animals with consistently reliable results. Likewise, tissues derived from the spleen, lung, lymph node and liver have been inoculated into small animals in order to establish the diagnosis of tularemia at post-mortem examination.

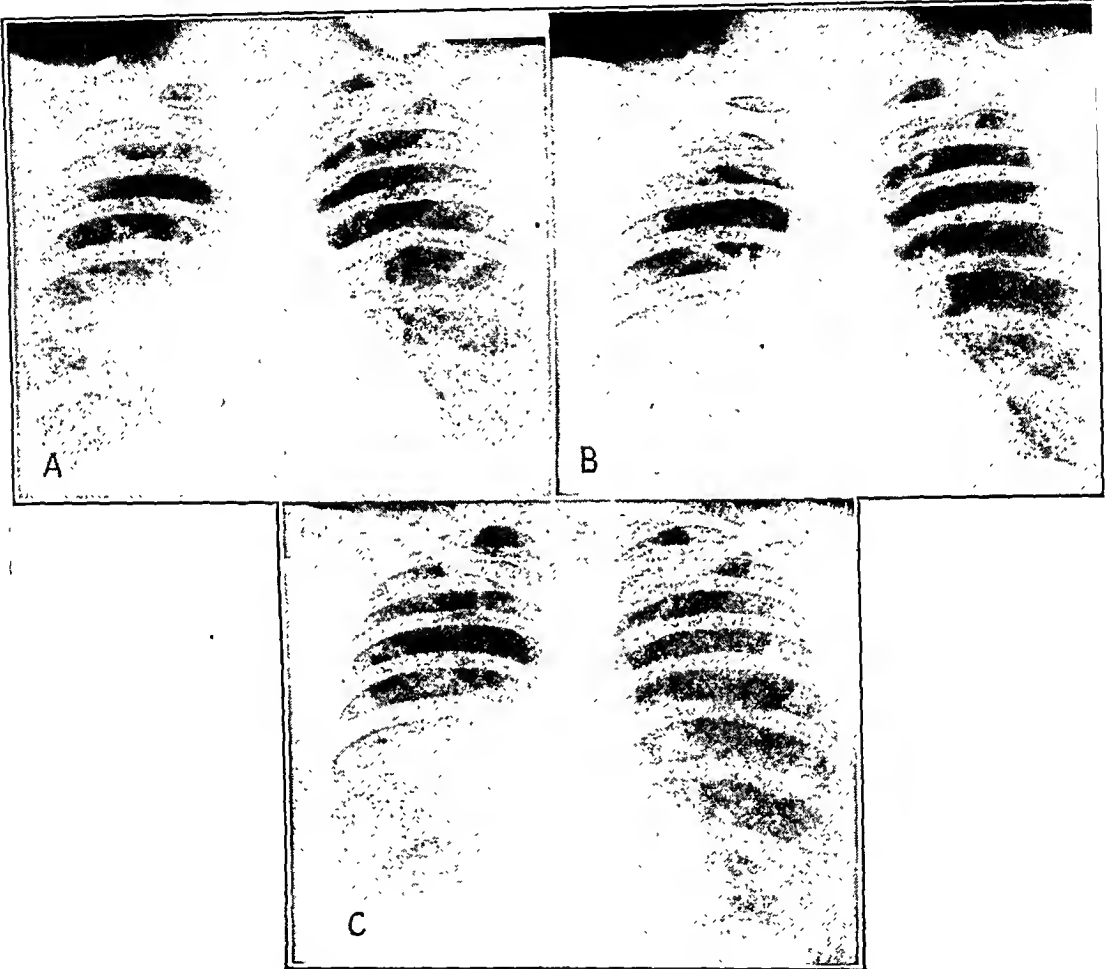


FIG. 1.—(Case 6.) The chest. *A*, On April 29, 1942, an opacity adjacent to lower pole of right hilum is clearly demarcated. Infiltration radiating from the hilum is seen. *B*, Four days later, the pneumonic consolidation has increased and extended to the periphery. *C*, On May 20, considerable resolution has occurred although a patchy, lobular involvement is still evident.

Other laboratory data are non-contributory to the diagnosis. The leukocyte count is usually within normal limits, although leukocytosis may occur infrequently. The red blood cell count is usually unaltered unless some other condition is present. The urine is generally normal except for a transient albuminuria associated with the more acute febrile stages of the disease.

The diagnosis both of tularemia and of tularemic pneumonia is frequently overlooked. In reviewing the literature, Kennedy<sup>39</sup> was impressed particularly with the lack of clinical recognition of the pulmonic form of tularemia.

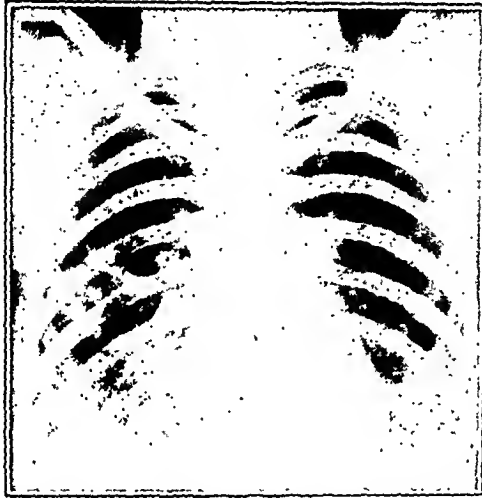


FIG. 2.—(Case 21.) The chest on Jan. 29, 1943. Numerous, discrete infiltrations throughout the right lung field typical of bronchopneumonia.

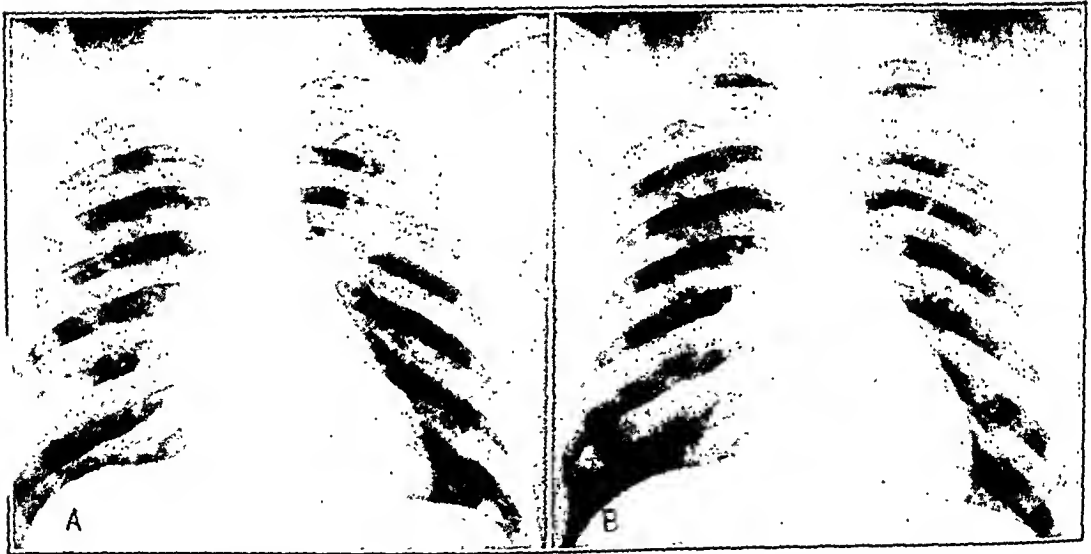


FIG. 3.—(Case 19.) A, The chest on Feb. 1, 1940, reveals an infiltration extending upward and outward from the left hilum which could be readily confused with pulmonary tuberculosis. B, Twenty days later, clearing of the previous infiltration.

**Course.** There is little question that tularemic pneumonia may be mild and transient in character, and frequently unrecognized except for roentgenographic evidence. In other cases, however, the pulmonic involvement is a manifestation of a widespread systemic infec-

tion and may contribute largely to the patient's death. As mentioned previously, pneumonia is found in the majority of cases at autopsy and, like tularemic peritonitis or pericarditis, its presence bears grave significance, especially if the involvement is bilateral. Of the 268 cases of tularemic pneumonia that we have collected from the literature (including 15 cases of our own), 161 cases recovered, resulting in a mortality rate of 39.9%.

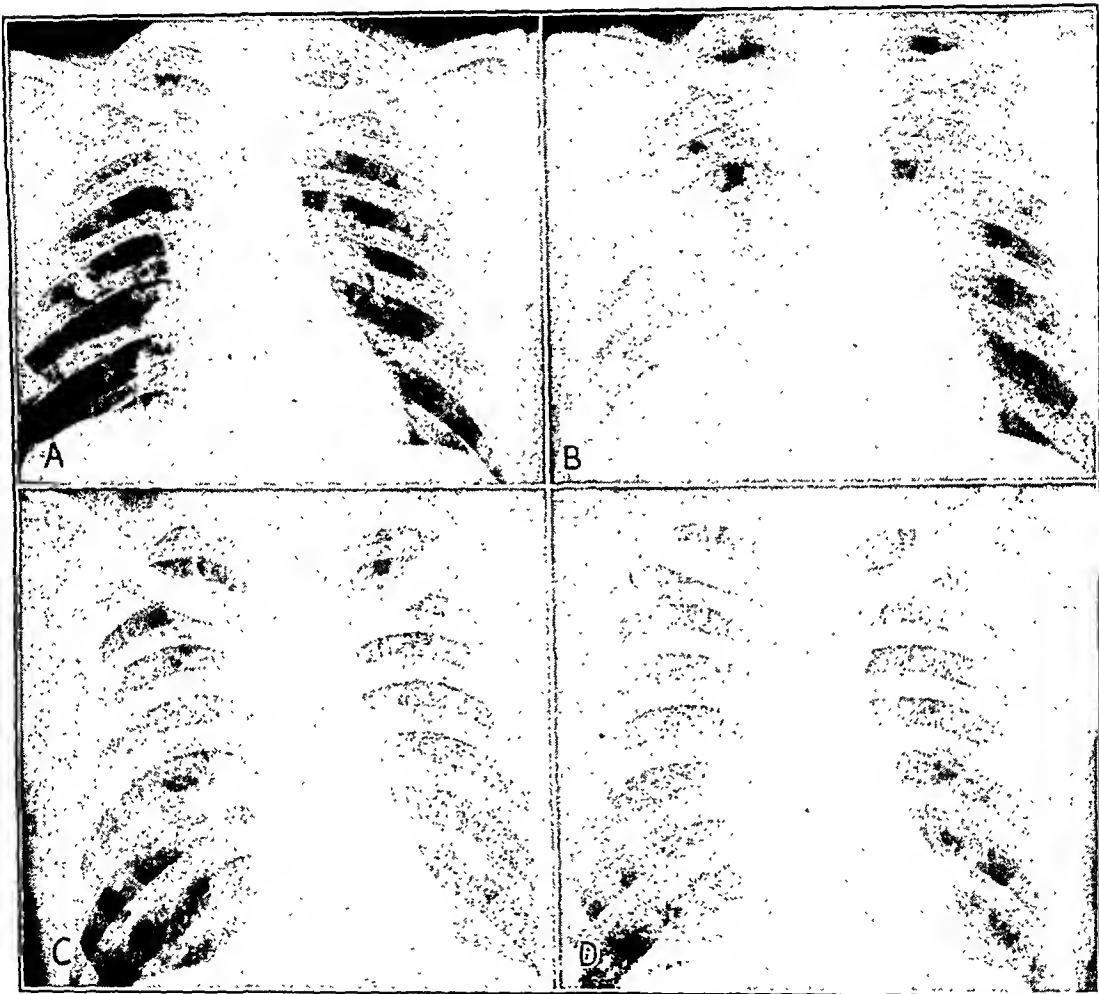


FIG. 4.—(Case 7.) The chest. A, On Jan. 28, 1944, slight enlargement of the hilar shadows and several small areas of bronchopneumonia in the right lung base are noted. B, Bilateral pneumonic involvement is clearly evident 15 days later. C, On May 24, numerous smaller areas of infiltration remain. D, On August 8, the lungs have cleared considerably, although some residual linear strands suggesting fibrosis remain.

The duration of the pneumonia is variable. It may last from a few days to several weeks. When the pulmonary involvement persists longer than 3 weeks, some complication, such as a lung abscess, secondary infection, or fibrosis, should be suspected.

**Treatment.** The specific treatment of tularemic pneumonia is a question that has not yet been finally answered. Specific immune

serum, according to Foshay,<sup>23</sup> is of aid in reducing the severity and duration of the symptoms, especially when given early in the disease, and may possibly be of assistance in treating tularemic pneumonia. Reports of several cases<sup>35,54,66</sup> treated with the sulfonamides have recently been published. Ransmeier,<sup>52</sup> however, found sodium sulfadiazine ineffective against *B. tularensis* as demonstrated experimentally *in vivo*. Although little data concerning the effectiveness of penicillin against *B. tularensis* have been collected thus far, it would appear that it is no more effective than other therapeutic agents generally available. It seems to us that unless evidences of secondary infection are found, such as a coëxistent pneumococcal pulmonary infection, that the treatment of tularemia and tularemic pneumonia is still largely supportive and symptomatic.

**Data.** We have recently reported our findings in a clinical study of 225 cases of tularemia observed at the Charity Hospital of Louisiana at New Orleans.<sup>50</sup> Of this group, 30 cases presented evidences of pneumonia, an incidence of 13.3%, while 7 cases had pleural effusion. In an effort to establish adequate criteria for the diagnosis of tularemic pneumonia, 9 of these cases were rejected. The present series, therefore, includes 21 cases of tularemic pneumonia, an incidence of 9.3%, while 4 of these cases had fluid in one or both pleural cavities. Six of the patients in this group have been previously reported by Moss and Weilbaecher,<sup>47,66</sup> hence we are reporting 15 additional cases. These cases have been summarized in Table 1.

In the selection of these patients, the following criteria for the diagnosis of tularemic pneumonia were observed: (1) autopsy with recovery of the organism from culture or animal inoculation; (2) aspiration biopsy of the lung with recovery of the organism from culture or animal inoculation; and (3) history of contact, positive physical signs of pneumonic consolidation with roentgenographic confirmation and rising blood agglutination titers for *B. tularensis*. Since routine roentgenograms of the chest were not made on all our patients with tularemia, and because of the fact that an occasional patient would present himself several weeks after the onset of the disease, it is quite probable that the incidence of pleuropulmonary tularemia in our series would have approached the figures given by Foshay<sup>23</sup> (17.8%) or Kavanaugh<sup>37</sup> (12.7%) had complete information been available on every patient.

Thirteen cases (61.9%) in this series had ulceroglandular tularemia with definite pulmonary involvement. However, only 7.1% of the total number of 181 cases of ulceroglandular tularemia observed at Charity Hospital developed pleuropulmonary tularemia. Eight cases (38.1%) were of the typhoidal type of tularemia and, in turn, 57% of the 14 cases of typhoidal tularemia at Charity Hospital had pulmonary involvement.

Twelve of these 21 patients gave a definite history of contact with rabbits. In 1 other patient, a 59 year old colored male farmer, the only history of exposure was that of a scratch inflicted by a rat. Of the remaining 8 patients from whom no history of contact was obtained, 7 were moribund on admission and expired without giving a satisfactory history.

TABLE 1.—CLINICAL DATA CONCERNING 21 CASES OF TULAREMIC PNEUMONIA

Case No.	Age	Color	Sex	Type of tularemia	Contact	Duration of symptoms before pneumonia (days)	Type of pneumonia	Associated findings	Diagnosis	Duration of pneumonia (days)	Remarks
1	59	C	M	U.G.	Rat	8	Broncho	Lues, cirrhosis	Rising agglut. titers	32	Recovered
2	33	W	M	U.G.	Rabbit	13	Broncho	....	Rising agglut. titers	15	Recovered
3	40	C	M	U.G.	Rabbits	Few hrs.	Broncho (bilat.)	Chr. cholecystitis	Animal inoc. (postm.)	1—	Autopsy
4	40	C	F	U.G.	Rabbits	12	Lobar	....	Rising agglut. titers	2	Death—no autopsy
5	58	W	F	U.G.	...	14	Broncho (bilat.)	Diabetes mellitus, nephrosclerosis	Rising agglut. titers, animal inoc. (postm.)	9	Autopsy; complication: uncontrolled diabetes mellitus
6	43	W	F	T.	Rabbit	14	Lobular	....	Rising agglut. titers	33	Recovered
7	59	C	M	T.	...	10	Broncho (bilat.)	....	Rising agglut. titers, lung aspir., biopsy; animal inoc.	22	Recovered
8	33	C	M	U.G.	Rabbit	21	Broncho	Lues	Rising agglut. titers	38	Recovered
9	32	C	F	U.G.	Rabbit	13	Broncho	Rt. pleural effusion	Rising agglut. titers	48	Recovered
10	33	W	M	U.G.	Rabbit	18	Broncho (bilat.)	....	Rising agglut. titers	24	Recovered
11	53	C	F	U.G.	...	10	Broncho (bilat.)	Thrombosis left femoral vein	Lung aspir., biopsy; animal inoc.	12	Death—no autopsy
12	34	C	M	T.	...	10	Broncho (bilat.)	Meningitis	Animal inoc. (postm.)	5	Autopsy
13*	22	C	M	T.	...	6	Broncho	Lung abscess	Animal inoc. (postm.)	4	Autopsy
14*	26	C	M	T.	Rabbit	8	Broncho (bilat.)	Rt. pleural effusion, Type VIII pneumococci in sputum	Animal inoc. (postm.)	2	Autopsy
15*	21	C	F	T.	...	...	Mult. abscesses	Malig. neutropenia	Animal inoc. (postm.)	2	Autopsy
16	50	C	F	T.	...	12	Broncho	Lues, cholelithiasis	Animal inoc. (postm.)	5	Autopsy
17	39	C	M	U.G.	Rabbit	9	Broncho	Benign prostatic hypertrophy; pleural effusion	Lung aspiration, biopsy; animal inoc.	3	Autopsy
18*	30	W	M	U.G.	Rabbit	12	Broncho (bilat.)	....	Rising agglut. titers	?	Probably recovered
19*	30	C	M	U.G.	Rabbit	9	Lobular	....	Rising agglut. titers, lung aspir., biopsy; animal inoc.	(deserted) 29	Recovered
20*	26	C	M	T.	...	9	Broncho (bilat.)	Lues; Type X pneumococci in sputum	Rising agglut. titers; animal inoc. (postm.)	19	Autopsy
21	27	C	F	U.G.	Rabbit	12	Broncho (bilat.)	Pl. effusion (bilat.)	Animal inoc. (postm.)	9	Autopsy

\* Denotes cases previously reported by other investigators.<sup>17,18</sup>



The occurrence of tularemic pneumonia in 13 males as compared to 8 females is proportional to the sex incidence for our entire group of tularemic patients (134 males and 91 females). The incidence of pulmonary involvement in 16 colored patients as compared to 5 white patients may be significant, however, inasmuch as 132 of the 225 tularemic patients studied were white as compared to 93 colored patients.

The occupational history revealed that two-thirds of this group consisted of housewives, farmers, cooks, butchers and peddlers and, as stated, was related to exposure to rabbits in all but 1 instance. In the remainder the occupation was such as to appear unrelated to the development of the disease.

The incubation period varied from 24 hours to 10 days in 12 cases in which an adequate history could be obtained. The average incubation period for this group was 4.5 days. It is of interest to compare this with Kavanaugh's observation<sup>37</sup> of 4.5 days in 123 cases of tularemia and Foshay's determination<sup>23</sup> of 3.3 days as the average incubation period of 600 collected cases of tularemia.

The duration of symptoms before the diagnosis of pneumonia was established varied from a few hours to 21 days, with an average of 11 days. The known duration of tularemic pneumonia in 12 cases before death varied from 22 hours in 1 instance to 19 days in another, while the average duration for this group was slightly more than 6 days. In 8 surviving cases the known duration of pulmonary involvement varied from 15 days in 1 case to a maximum of 48 days in another, with, however, an average of 30 days. One patient deserted the hospital before complete recovery.

The diagnosis of tularemic pneumonia was definitely established in 8 patients that eventually recovered by demonstrating rising blood agglutination titers for *B. tularensis*. Three patients were diagnosed in a similar manner before death. Aspiration biopsy of the lungs with guinea pig inoculation confirmed the diagnosis in 2 patients that subsequently recovered from the disease and 1 that succumbed. Eight of the group had no definite diagnosis before necropsy was performed; in 4 of these patients, however, tularemia was suspected because of the presence of primary lesions and lymphadenopathy or a definite history of handling rabbits.

Nine of our 21 patients recovered from the disease while 12 died, a mortality rate of 57% in 21 cases of tularemic pneumonia. Autopsies were secured on 10 patients. Curiously, 6 of 8 females with tularemic pneumonia expired, whereas only 6 of 13 males in this series died. The only white patient (a female) that died probably expired as a result of uncontrolled diabetes mellitus, and the death of 1 colored female may possibly be attributed to a malignant neutropenia following sulfonamide therapy.<sup>47</sup>

In addition to the sex factor, a racial predisposition was noted. Thus, 11 of the 12 deaths were in Negroes, a mortality rate of 69% of the 16 colored patients in our group.

**Summary.** 1. Up to September 1944, 253 cases of tularemic pneumonia were collected from the American literature and we have reported 15 additional cases herein.

2. Criteria for the diagnosis of tularemic pneumonia have been outlined.

3. Of 225 cases of tularemia observed at the Charity Hospital of Louisiana at New Orleans, 21 cases (9.33%) had accompanying tularemic pneumonia.

4. The incidence of tularemic pneumonia is distinctly greater in the typhoidal forms than in the ulceroglandular types of tularemia. Thus, only 13 (7.1%) of 181 cases of ulceroglandular tularemia developed pleuropulmonary involvement, whereas 8 cases (57%) of 14 instances of typhoidal tularemia developed clinical tularemic pneumonia.

5. Of our 21 patients with tularemic pneumonia, 12 (57%) expired.

6. Although our incidence of tularemia in colored patients as compared to white patients is proportional to the total admissions of white and colored patients at Charity Hospital for the same period of time, it would seem from our findings that Negroes are particularly lacking in resistance once they have developed the pulmonic forms of the disease. This is evidenced by the fact that 16 of our 21 cases of tularemic pneumonia were colored and that 11 of these 16 patients expired. Whether this racial susceptibility is due to lack of immunity, or inability to develop immune bodies, or whether environmental, dietary and other factors associated with a lower standard of living are responsible is a question that we must leave unanswered. Only 1 white patient expired, and this may be attributed in part to an uncontrolled diabetes mellitus.

7. Curiously, 6 of 8 women with tularemic pneumonia died, as compared to 6 of 13 men. Analysis of the charts suggests that the sex predisposition may have been coincidental.

8. In patients who recovered, the average duration of the pneumonia was 30 days, attesting, therefore, to the marked morbidity as well as mortality of this disease.

9. No specific therapy in our hands has been beneficial. The patient should be supported until the disease has run its course.

10. Every patient with tularemia should be observed carefully both clinically and roentgenographically for the development of pleuropulmonary tularemia. Such patients should, of course, be isolated.

#### REFERENCES

1. AAGAARD, G. N.: *Minnesota Med.*, **27**, 115, 1944.
2. ALLEN, H. G., and SMITH, M. G.: *Arch. Path.*, **26**, 1052, 1938.
3. AMOSS, H. L., and SPRUNT, D. H.: *J. Am. Med. Assn.*, **109**, 264, 1937.
4. BARDON, R., and BERDEZ, G.: *J. Am. Med. Assn.*, **90**, 1369, 1928.
5. BERNSTEIN, A.: *Arch. Int. Med.*, **56**, 1117, 1935.
6. BIHSS, T. E., and BERLAND, H. L.: *Radiology*, **41**, 431, 1943.
7. BLACKFORD, S. D.: *Trans. Am. Clin. and Climatol. Assn.* (1937), **53**, 92, 1939.
8. BLACKFORD, S. D.: *Ann. Int. Med.*, **5**, 1421, 1932.
9. BLACKFORD, S. D.: *J. Am. Med. Assn.*, **104**, 891, 1935.
10. BLACKFORD, S. D., and ARCHER, V. W.: *J. Am. Med. Assn.*, **109**, 264, 1937.
11. BLACKFORD, S. D., and CASEY, C. J.: *Arch. Int. Med.*, **67**, 43, 1941.

12. BLUMBERG, A., and RUSSELL, R. L.: *Med. Bull. Vet. Admin.*, 11, 77, 1934.
13. BOMAN, P., and BIANCO, H. J.: *Ann. Int. Med.*, 7, 1491, 1934.
14. BRYANT, A. R., and HIRSCH, E. F.: *Arch. Path.*, 12, 917, 1931.
15. BUNKER, C. W. O., and SMITH, E. E.: *U. S. Nav. Med. Bull.*, 26, 901, 1928.
16. CHAUDRON, P. O.: *J. Med. Assn. Georgia*, 30, 11, 1941.
17. DAVID, J. K., and OWENS, J. N.: *Am. J. Dis. Child.*, 67, 44, 1944.
18. DREDGE, T. E.: *Med. Bull. Vet. Admin.*, 16, 337, 1940.
19. ELLIOTT, W. G.: *J. Med. Assn. Georgia*, 30, 401, 1941.
20. FETTERMAN, G. H., and LERNER, H.: *J. Lab. and Clin. Med.*, 21, 1157, 1936.
21. FINNEY, J. O.: *South. Med. J.*, 35, 660, 1942.
22. FLINN, L. B.: *Delaware State Med. J.*, 7, 219, 1935.
23. FOSHAY, L.: *Medicine*, 19, 1, 1940.
24. FOULGER, M., GLAZER, A. M., and FOSHAY, L.: *J. Am. Med. Assn.*, 98, 951, 1932.
25. FRANCIS, E.: *J. Am. Med. Assn.*, 91, 1155, 1928.
26. FRANCIS, E.: in Cecil, R. L., *Textbook of Medicine*, Philadelphia, Saunders, p. 350, 1938.
27. GIBBONS, E. H., LAMOUREAUX, E. L., and ARKLESS, H. A.: *Connecticut Med. J.*, 5, 679, 1941.
28. GUDGER, J. R.: *J. Am. Med. Assn.*, 101, 1148, 1933.
29. GUNDRY, L. P., and WARNER, C. G.: *Ann. Int. Med.*, 7, 837, 1934.
30. HARTMAN, F. W.: *Am. J. Path.*, 8, 57, 1932.
31. HARTMAN, H. R., BEAVER, D. C., and GREEN, R. G.: *Minnesota Med.*, 16, 559, 1933.
32. HUBIN, E. G.: *Jour.-Lancet*, 57, 289, 1937.
33. HUGHES, J. D., and HUGHES, J. G.: *Memphis Med. J.*, 15, 161, 1940.
34. JAGER, B. V., and RANSMEIER, J. C.: *Bull. Johns Hopkins Hosp.*, 72, 166, 1943.
35. JOHNSTON, J. M.: *J. Am. Med. Assn.*, 115, 1360, 1940.
36. JUNGHER, E.: *J. Bact.*, 43, 643, 1942.
37. KAVANAUGH, C. N.: *Arch. Int. Med.*, 55, 61, 1935.
38. KAVANAUGH, C. N.: *Internat. Clin.*, 2, 200, 1941.
39. KENNEDY, J. A.: *J. Am. Med. Assn.*, 118, 781, 1942.
40. KIMMELSTIEL, P., and CALDWELL, H. W.: *Am. J. Path.*, 15, 127, 1939.
41. LEWY, R. B.: *Illinois Med. J.*, 70, 192, 1936.
42. LILLIE, R. D., and FRANCIS, E.: *Bull. 167, Nat. Inst. of Health* (February), 1936.
43. MASSEE, J. C.: *J. Med. Assn. Georgia*, 20, 66, 1931.
44. MATTHEWS, W. R.: *New Orleans Med. and Surg. J.*, 90, 479, 1938.
45. MCCOY, G. W.: *U. S. Pub. Health Bull.*, No. 54, p. 17, 1911.
46. MOORE, F. D., SAWYER, C. S., and BLOUNT, S. G.: *New England J. Med.*, 231, 169, 1944.
47. MOSS, E. S., and WEILBAECHER, J. O.: *South. Med. J.*, 34, 512, 1941.
48. PERMAR, H. H., and MACLACHLAN, W. W. G.: *Ann. Int. Med.*, 5, 687, 1931.
49. PESSIN, S. B.: *Arch. Int. Med.*, 57, 1125, 1936.
50. PULLEN, R. L., and STUART, B. M.: *J. Am. Med. Assn.* In press.
51. PUND, E. R., and HATCHER, M. B.: *Ann. Int. Med.*, 10, 1390, 1937.
52. RANSMEIER, J. C.: *J. Infect. Dis.*, 72, 83, 1943.
53. REIMANN, H. A.: *The Pneumonias*, Philadelphia, Saunders, p. 277, 1938.
54. RICHARDS, G. G.: *Ann. Int. Med.*, 17, 78, 1942.
55. SANTE, L. R.: *Am. J. Roent. and Rad. Ther.*, 25, 241, 1931.
56. SIMPSON, W. M.: *Arch. Path.*, 6, 553, 1928.
57. SIMPSON, W. M.: *Tularemia*, New York, Hoeber, 1928.
58. SLOAN, L. H., FREEDBERG, A. S., and EHRLICH, J. C.: *J. Am. Med. Assn.*, 107, 117, 1936.
59. STOFER, D. D.: *Ann. Int. Med.*, 12, 407, 1938.
60. STUMP, D., and QUINN, F.: *J. Kansas Med. Soc.*, 41, 426, 1940.
61. SUDGEN, J. W.: *Northwest. Med.*, 34, 167, 1935.
62. TERRY, L. L., and REICHEL, H. S.: *Arch. Path.*, 29, 473, 1940.
63. THOMAS, H. B.: *Ann. Int. Med.*, 17, 659, 1942.
64. TUREEN, L. L.: *J. Am. Med. Assn.*, 99, 1501, 1932.
65. VERBRYCKE, J. R.: *J. Am. Med. Assn.*, 82, 1577, 1924.
66. WEILBAECHER, J. O., and MOSS, E. S.: *New Orleans Med. and Surg. J.*, 92, 694, 1940.
67. WEILBAECHER, J. O., and MOSS, E. S.: *J. Lab. and Clin. Med.*, 24, 34, 1938.
68. WINTER, M. D., FARRAND, B. C., and HERMAN, H. J.: *J. Am. Med. Assn.*, 109, 258, 1937.
69. ZIFFERSTEIN, I.: *J. Iowa Med. Soc.*, 30, 65, 1940.

OSTEOMYELITIS CAUSED BY GRANULOMA INGUINALE  
REPORT OF A CASE WITH CULTIVATION OF THE DONOVAN BODY  
IN THE YOLK SACK OF THE DEVELOPING CHICK EMBRYO

By WALTER H. SHELDON, M.D.

BEN R. THEBAUT, M.D.

ALBERT HEYMAN, M.D.

AND

MARGARET J. WALL

ATLANTA, GA.

(From the Departments of Pathology, Surgery, and Medicine of Grady Memorial Hospital and Emory University School of Medicine)

ALTHOUGH extragenital lesions of granuloma inguinale are not uncommon (lip, mouth, neck, etc.), visceral manifestations of this condition have been reported in but few instances.<sup>6</sup> Skeletal involvement by granuloma inguinale has been noted in only 9 cases.<sup>4,7-13</sup> Since bone lesions are unusual, this case of osteomyelitis of the tibia is reported. Donovan bodies were found in histologic section of biopsies from this case and were cultivated in the yolk sac of developing chick embryos by the method described by Anderson and co-workers.<sup>1-3</sup>

Extragenital lesions of granuloma inguinale are generally believed to be the result of contact infection. Occasionally, however, multiple extragenital lesions are found and their widespread distribution has suggested a hematogenous dissemination.<sup>11</sup> Both the older references of widespread visceral involvement of granuloma inguinale and the more recently reported cases of osteomyelitis complicating genital lesions seem to support this idea of a systemic disease. In many of these cases bone lesions were found in the extremities, thorax, and skull but there were no skin ulcerations. In these patients the spread of the disease by the blood stream must be admitted. That the disease may be systemic is suggested by the following case in which a primary extragenital lesion appeared several weeks before the genital ulcer.

Cultivation of Donovan bodies on bacteriologic media has been unsuccessful<sup>6</sup> and diagnosis depended upon the finding of the organism in spreads or histologic sections. However, 2 new methods of isolating the Donovan body have been reported: one by continuous tissue culture,<sup>9</sup> and the other by the use of the yolk sac of the chick embryo, as described by Anderson.<sup>1</sup> The latter method was successfully employed in this case.

**Case Report.** C. S., a 43 year old colored male, was admitted to the Orthopedic Service on September 19, 1944, complaining of a sore on his leg. About 6 months before admission he struck his left shin and sustained a bruise which persisted. Three months prior to admission he again injured the bruised area and an ulcer formed. This ulcer gradually increased in size, without local pain or tenderness. One month after the onset of ulceration the patient noticed that the left knee was becoming stiff, although there was no pain on motion. During the month prior to admission the left leg was occasionally painful.

Three weeks before admission the patient first noticed a penile lesion. This

consisted of a small erosion of the dorsum of the shaft of the penis adjacent to the corona. This ulcer gradually spread to involve the circumference of the penis. There was no local pain or tenderness.

The ulceration of the left leg did not confine the patient to bed but he had to walk with a crutch. His appetite remained good, but his weight dropped from 130 to 86 pounds. There were no other systemic symptoms.

The patient gave a history of urethral discharge 20 years ago. This was complicated by a left inguinal bubo which ruptured spontaneously, drained for a short time, and then healed. About 18 years ago he had a lesion on the frenulum of the penis which healed without treatment. He had never had a serologic test or treatment for syphilis.



FIG. 1.—The lesion of *granuloma inguinale* proximal to the corona of the penis.

The patient denied extramarital sexual contacts during the past year. He stated that his wife had no visible genital lesions.

Despite repeated questioning, the patient insisted that the ulcer on the leg had been present for a long time before the penile lesion appeared.

Physical examination revealed an emaciated, middle-aged colored male whose appearance suggested considerable recent weight loss. The mucous membranes and palms exhibited moderate pallor. His temperature was 98.8° F. on admission, and the pulse and respiration were normal. The blood pressure was 100/80. The skin was loose and lacked normal elasticity. The eyes, ears and nose and throat showed no abnormality. The neck, heart, lungs and abdomen were also normal. There was a scar with slight keloid formation in the left inguinal region.

The penis was circumcised and showed a non-tender, band-shaped ulcer encircling the organ just proximal to the corona. The ulcer measured from 1 to 2 cm. in width. The lesion consisted of red, velvety, friable granulation tissue with sharply demarcated, slightly elevated edges (Fig. 1).

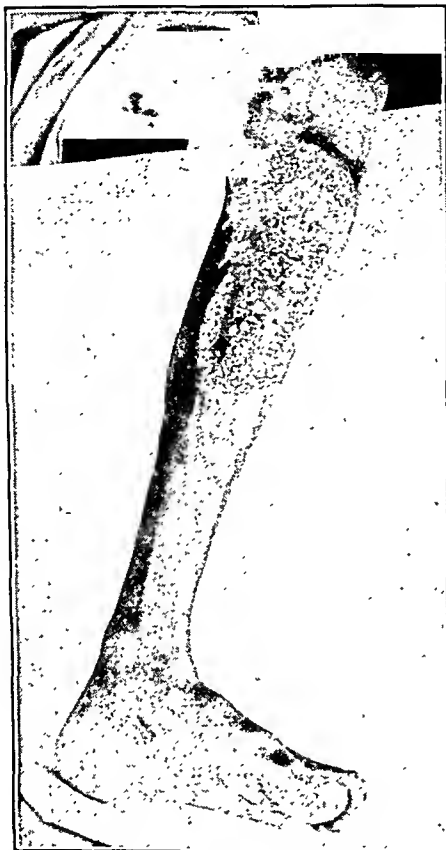


FIG. 2.—The large granulomatous lesion of the left leg. Note the deep ulceration near the upper edge of the lesion which extended into the marrow cavity of the tibia.

The left upper shin showed a large, tender, elevated granulomatous lesion, measuring about 7 x 15 cm. The granulations were exuberant and friable. In the upper portion of the lesion there was a deep, funnel-shaped ulcer about 3.5 cm. in diameter which extended into the medullary cavity of the tibia (Fig. 2).

In the right inguinal region several small, discrete, non-tender lymph nodes were felt; none was noted in the left groin.

The laboratory findings were: R.B.C. count, 4,050,000, with 9.6 gm. of hemoglobin; W.B.C. count, 6200, with a normal differential; urine negative; blood Kahn negative; sedimentation rate 125 mm. in 1 hour. There was no evidence of sickling of the erythrocytes. The blood calcium was 12 mg. per 100 cc.; blood phosphorus, 4 mg. per 100 cc.; serum alkaline phosphatase, 4.6 Bodansky units; total serum protein, 7.7 gm. per 100 cc. Spinal fluid studies revealed nothing abnormal. Ducrey and tuberculin skin tests were positive. The Frei test was negative, but the complement-fixation test for lymphogranuloma venereum was positive to a titer of 1:80.

Roentgenograms of the left leg showed a large bone defect in the proximal tibia at the level of the tubercle. This defect measured about 4 cm. in diameter and extended from the anterior surface of the tibia to its posterolateral aspect,

resulting in dissolution of the cortex. This bone cavity was surrounded by moderate sclerosis. There was irregular periosteal thickening along the medial, lateral, and posterior aspects of the proximal tibia. The width of the knee joint was slightly reduced and the distal femur and tibial condyles showed moderate osteoporosis. The articular surfaces of the tibia and femur were intact. There was no evidence of bony ankylosis. The roentgenologist stated that the findings were consistent with a chronic infection (Fig. 3).



FIG. 3.—Roentgen ray of left tibia, lateral and antero-posterior view. Note the large defect in the tibia with some sclerosis of the surrounding bone and irregular periosteal thickening.

Roentgenograms of other bones were negative except for a cystlike area of rarefaction, measuring 1 x 1.5 cm. in the anterior portion of the 7th rib on the left side. The area of rarefaction was surrounded by a zone of sclerosis and there was no periosteal reaction.

The preliminary clinical impression was that of a tumor of the left tibia. Biopsies from the granulation tissue of the leg and later from the penis showed granuloma inguinale. Two attempts to isolate Donovan bodies from the penile lesion by means of the yolk sac method were unsuccessful because of bacterial contamination. After local applications of a solution of tyrothricin and of sulfanilamide powder in an attempt to eliminate the secondary infection, an osteotomy of the left tibia was done. Biopsies from surface granulation tissue, bone and bone marrow showed granuloma inguinale on histologic section. Donovan bodies were isolated in pure culture by inoculation into yolk sacs of a portion of this material.

Biopsy of the rib lesion was done on the 23rd hospital day, but the specimen did not show granuloma inguinale either by histologic study or yolk sac inoculation.

Treatment consisted of the local application of sulfanilamide powder and tyrothricin to the leg and penile lesions. The tibial defect was packed with iodoform gauze, and the packing changed at frequent intervals. Sulfadiazine was administered orally. Fuadin was given intramuscularly at weekly intervals.

On the 29th hospital day a split-thickness skin graft was applied to the lesion of the left leg. Approximately 90% of the grafted skin survived.

The patient remained in the hospital for 48 days. During the entire period

his temperature never rose above 99° F. He was dismissed 20 days after the skin graft was applied and is now being followed in the out-patient clinic.

The leg lesion is now completely epithelialized except in the area immediately overlying the bone defect. This area is slowly filling in with granulation tissue. The penile lesion shows some healing. Treatment with fuadin is being continued.

*Report of Biopsy Material.* The various fragments of tissue obtained by biopsy were of reddish-tan color and of meaty consistency. Fragments of bone were attached to the specimens from the tibia and its marrow.

All tissues were fixed immediately in Zenker's fluid with 5% glacial acetic acid and in a 10% solution of formalin U.S.P. Eleven sections stained with phloxine-methylene blue were examined.

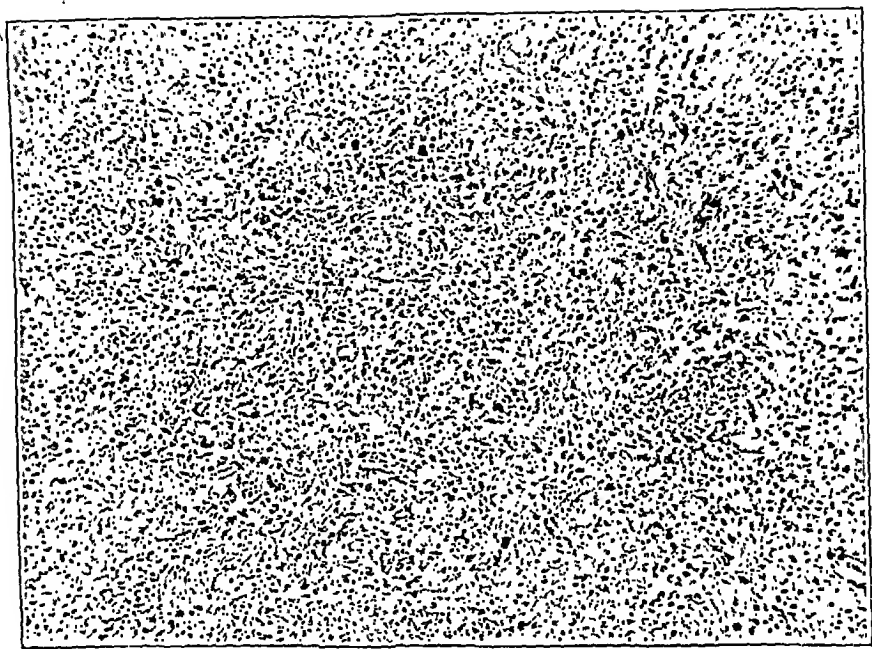


FIG. 4.—The granulation tissue with microabscesses from the lesion of the leg. This general pattern is quite suggestive of granuloma inguinale. Phloxine-methylene blue X 105.

The histologic picture was the same in the various tissues. It consisted of richly vascularized granulation tissue with marked inflammatory cell infiltration (Fig. 4). There were numerous plasma cells and lymphocytes, but there was a predominance of large mononuclear cells and neutrophilic polymorphonuclear leukocytes. The polymorphonuclear leukocytes were scattered throughout the tissue or formed small and medium sized microabscesses. The large mononuclear cells were dispersed throughout the tissue and showed a finely reticulated or vacuolated cytoplasm. Phagocytosis of polymorphonuclear leukocytes and other cellular debris by these cells was common.

A large number of the mononuclear cells contained typical Donovan bodies. Sometimes as many as 8 cells laden with Donovan bodies were encountered in a single oil immersion field. These infested cells were most numerous at the periphery of the microabscesses but were also found elsewhere. All stages of infestation were noted in these cells. Sometimes only small groups of Donovan bodies occupied a part of the cytoplasm, while in other instances the entire cell body was invaded. In some cells the cytoplasm appeared cystic; in others rupture of the cell body had occurred.



Some proliferation of fibroblasts and deposition of collagen was encountered in a few areas, but this process had not progressed significantly.

The sections of the bone and bone marrow showed spicules of degenerating and necrotic bone without appreciable new bone formation.

The epidermis at the edges of the lesion was necrotic and infiltrated by polymorphonuclear leukocytes. There was no regeneration.

Numerous mononuclear cells laden with Donovan bodies were seen on the ulcerated surface of the lesion together with occasional cocci. No microorganisms were identified elsewhere in the sections.

*Cultivation of Donovan Bodies.* The surface granulation tissue, bone marrow, and adjacent tissue were all found to contain Donovan bodies on impression smears stained by Wright's method. The organisms were grown from the surface granulation tissue in the yolk sac of chick embryos by the method described by Anderson and co-workers.<sup>1,2,3</sup> Cultures on blood agar and in thioglycollate revealed no bacteria in the inoculum or in the material harvested from eggs. From bone marrow and adjacent tissue, however, Donovan bodies were not isolated because the inoculum contained a slowly growing alpha streptococcus which killed the chick embryos.



FIG. 5.—Impression smear of granulation tissue adjacent to the tibia. A large mononuclear cell with numerous typical Donovan bodies. The cytoplasm of this cell is characteristically vacuolated. Wright stain  $\times 1000$ .

The details of the cultivation of the Donovan bodies are as follows: Granulation tissue from beneath the surface of the lesion was triturated in a mortar and made into a 10% suspension with saline solution. Following a low-speed centrifugation, the supernatant material was injected in 0.6 cc. amounts into the yolk sacs of 15 6-day-old embryos. The eggs were then reincubated at 37° C. Three embryos were dead the following day and were discarded. Two died on the 2nd day and were also discarded because impression smears of their yolk sacs revealed no microorganisms. Smears of yolk and yolk sacs harvested from living embryos on the 2nd, 3rd and 4th days showed progressively increasing numbers of Donovan bodies. The remaining eggs were harvested on the 7th and 11th days and were found to contain a few clusters of intracellular bodies. Second passage of the agent was initiated with material taken on the 4th day. A yolk sac was mixed with yolk from the same egg, shaken with glass beads on a shaking machine, and inoculated in 1 cc. amounts into 11 6-day-old embryonated eggs. This 2nd passage produced a moderate growth of Donovan bodies by the 3rd day and a rich yield on the 4th day. Successive passages of the agent shortened the incubation period to 3 days, so that harvests made at this time contained a large number of bodies. Eight serial passages were made and in each one the Donovan bodies presented the same

morphology. Bacteriologic cultures on blood agar, in thioglycollate, and occasionally in tryptose-phosphate broth containing agar, yielded no growth from yolk or membranes of each passage.

The morphology of Donovan bodies was observed by impression smears of human and yolk sac material, stained by Wright's method. With spreads of infected yolk, flooding the slide with ethyl ether before staining removed much of the yolk and consequently facilitated the search for Donovan bodies. The morphology of the organisms was not changed by this procedure. Touch smears of human granulation tissue revealed the bodies to be of variable morphology. They consisted chiefly of forms resembling closed "safety pins," diplococcal forms or encysted clusters of single bodies, with a few encapsulated organisms present. The majority of them occurred intracellularly (Fig. 5). When cultivated in embryonated eggs, the Donovan bodies were shown to have a morphology similar to that seen in smears of human material. "Safety pin" and shorter, bipolar forms predominated, although curved rods and encapsulated types were often observed in the same preparation (Fig. 6).

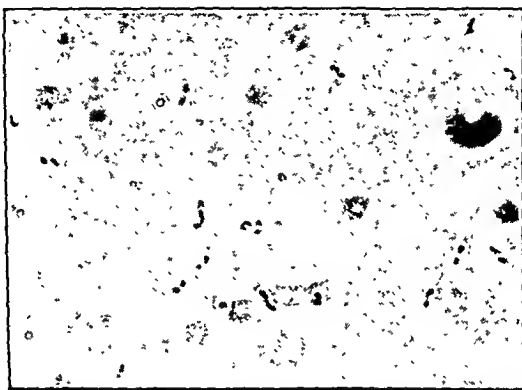


FIG. 6.—Donovan bodies in a spread of yolk infected with the fourth passage of the agent cultivated in embryonated eggs. Wright stain  $\times 1000$ .

**Discussion.** The occurrence of osteomyelitis caused by granuloma inguinale is uncommon. We have found only 4 cases in the literature in which the diagnosis was proven by histologic examination.<sup>9,11</sup> The other cases<sup>10,12,13</sup> must be regarded as less authenticated, for the diagnosis of granuloma inguinale was based entirely on the isolation of bacteria thought to be the etiologic agent. These latter case reports describe widespread visceral involvement with multiple granulomatous abscesses of the bone, liver, lungs, spleen and intestine.<sup>6-8,12,13</sup> There are recent reports, however, of arthritic manifestations with extensive lesions in the joints of the hands and feet.<sup>9</sup>

In some of the reported cases there was an extension of the skin granuloma into the underlying bone, while in others the skin ulceration was secondary to the breakdown of the bone lesion. In our case, we could not be certain whether the bone or skin was the primary site of the extragenital lesion, for both tissues were involved when the patient was first seen.

In the majority of cases reported a moderate amount of local pain and tenderness was present over the bone lesions. There were rarely any signs of an acute inflammatory process. Generally, systemic symptoms of malaise, weight loss, low grade fever, and anemia were

noted. The patients usually pursued a chronic course of remissions and relapses. Among the proven cases only 1 death occurred.<sup>9</sup>

Occasionally an elevation of the serum globulin and of the alkaline phosphatase level was noted. The roentgenograms usually revealed a lytic bone lesion with little evidence of new bone formation. This was also found in our patient, in which there appeared only a slight sclerosis about the area of destruction. In some instances the bone lesions responded to antimony therapy,<sup>11</sup> while in 1 case successive amputations were necessary before the infection could be controlled.<sup>9</sup>

The diagnosis of bone involvement is usually made by finding Donovan bodies in impression smears or histologic sections. The organism was reported to be isolated in continuous tissue culture from one of the cases reported by Lyford *et al.*<sup>9</sup> In our patient the organism was cultivated in the yolk and yolk sac of chick embryos from the granulation tissue of the leg. In our work the technique described by Anderson provided a useful means of demonstrating this organism. Anderson and co-workers<sup>2,3</sup> have recently published reports which conclusively indicate that the Donovan body is the etiologic agent of granuloma inguinale. Donovan bodies were not isolated from the tibia because of bacterial contamination of the biopsied specimen, although they were found in smears and histologic sections of the bone. The cystic lesion of the rib was suspected of being granuloma inguinale, but showed no evidence of this condition in either histologic sections, or yolk sac cultures.

Our patient insisted that the leg ulcer appeared 9 weeks before the onset of the genital lesion. We cannot be certain of the pathogenesis or of the sequence of events in this patient. The leg ulcer might represent a primary extragenital lesion with secondary contact infection of the penis. It is also possible that the penile lesion was present at the same time as the leg ulcer, but was too small to be noticed by the patient. In either event the patient's and the physician's attention was directed to the leg lesion. The correct diagnosis was not suspected clinically, but was made by biopsy of the leg ulcer.

The possibility of extragenital granuloma inguinale should be considered in cases of chronic skin ulceration and even in non-healing osteomyelitis, regardless of location. Just as in syphilitic infection, the absence of a genital lesion need not exclude the possibility of systemic granuloma inguinale. It is striking that all proven cases of skeletal granuloma inguinale have been reported within the past year. Once it is realized that systemic manifestations of this disease occur, other instances of disseminated granuloma inguinale will be noted.

**Summary.** 1. A case of osteomyelitis of the tibia caused by granuloma inguinale is reported.

2. Donovan bodies from this case were cultivated in the yolk and yolk sac of the chick embryo according to the method described by Anderson.

3. A review of the literature reveals that bone involvement by granuloma inguinale is rare, but when found may be a manifestation of the systemic nature of this disease.

## REFERENCES

1. ANDERSON, K.: *Science*, **97**, 560, 1943.
2. ANDERSON, K., DE MONBREUN, W. A., and GOODPASTURE, E. W.: *J. Exp. Med.*, **81**, 25, 1945.
3. ANDERSON, K., GOODPASTURE, E. W., and DE MONBREUN, W. A.: *J. Exp. Med.*, **81**, 41, 1945.
4. BECKER, W. S.: In discussion of Greenblatt.<sup>5</sup>
5. GREENBLATT, R. B., DIENST, R. B., PUND, E. R., and TORPIN, R.: *J. Am. Med. Assn.*, **113**, 1109, 1939.
6. GREENBLATT, R. B., TORPIN, R., and PUND, E. R.: *Arch. Derm. and Syph.*, **38**, 358, 1938.
7. HOFFMAN, W. H.: Quoted by Greenblatt.<sup>5</sup>
8. KUHN: *Berl. klin. Wchnschr.*, **43**, 435, 1906.
9. LYFORD, J., 3rd, SCOTT, R. B., and JOHNSON, R. W., JR.: *Am. J. Syph. Gon. and Ven. Dis.*, **28**, 588, 1944.
10. MAYER, M., and DA ROCHA LIMA, H.: *Hand. d. Haut u. Geschlechtskr.*, **21**, 433, 1927.
11. PAGGI, L. C., and HULL, E.: *Ann. Int. Med.*, **20**, 686, 1944.
12. THIERFELDER, M. U.: *Arch. f. Schiffs- u. Tropen-hyg.*, **29**, 690, 1925.
13. THIERFELDER, M. U., and THIERFELDER-THILLOT, M.: *Arch. f. Schiffs- u. Tropen-hyg.*, **28**, 221, 1924.

## HEMOCHROMATOSIS ASSOCIATED WITH PRIMARY ADENOCARCINOMA OF THE LIVER

### A CASE ILLUSTRATING DIAGNOSTIC FEATURES

BY J. A. OSHLAG, M.D.

PASSED ASSISTANT SURGEON (R), UNITED STATES PUBLIC HEALTH SERVICE  
MOBILE, ALA.

AND

R. F. MARTIN, M.D.

SURGEON, UNITED STATES, PUBLIC HEALTH SERVICE  
CRYSTAL CITY, TEX.

With Pathologic Report by C. H. BINFORD, M.D.

SURGEON, UNITED STATES PUBLIC HEALTH SERVICE  
NEW ORLEANS, LA.

(From the United States Marine Hospital, Mobile, and Laboratory, United States  
Marine Hospital, New Orleans)

It has been noted in several pertinent papers of the past 13 years that primary carcinoma of the liver complicates some 7% of cases of hemochromatosis. Yet, because of the rarity of hemochromatosis, the total number of cases occurring with associated primary hepatic carcinoma is small. Berk and Lieber,<sup>1</sup> in 1941, by adding 3 cases of their own to a previously reported 29, brought the total number of acceptable cases to 32. Since then, and up until the end of September 1943, Willis<sup>4</sup> has added 3 and Saward<sup>3</sup> 1 case. With the case herewith reported, the recorded number of cases of hemochromatosis with primary carcinoma of the liver mounts to 37.

Correct preoperative or antemortem diagnosis of these diseases in association has not been made, to the best of our knowledge. Careful consideration of the symptoms produced directly by the malignancy and of the variations in the expected course of hemochromatosis, which appear following the development of malignancy, should, however, lead to correct diagnosis. The diagnostic features have been set forth

and thoroughly reviewed in a recent communication.<sup>1</sup> Briefly, the symptoms which should lead to suspicion of hepatoma complicating hemochromatosis are: rapid progression of symptoms; abdominal pain as an outstanding complaint; jaundice; ascites, particularly sanguinous and not occurring as a terminal phenomenon; a massive liver, hard in consistency and nodular, or with disproportionate enlargement of the right lobe; amelioration of severity of the diabetes with undue liability to hypoglycemia; fever; anemia; leukocytosis; loss of weight; and evidence of metastatic involvement in lungs or other organs.

Of these symptoms some, notably pain, jaundice, ascites, and loss of weight (due to uncontrolled diabetes), are seen in uncomplicated hemochromatosis, but so rarely as to make their appearance strongly suspicious of the presence of an added neoplastic factor.

The case reported below presents many of these diagnostic features.

**Case Report.** J. M., a Filipino, aged 48, a ship's steward, was admitted to the hospital on Jan. 29, 1944. Family history was unknown to him and previous diseases were denied, with the exception of gonorrhea and syphilis about 1933, both apparently adequately treated.

Patient stated that he had been in good health up until 1 month before admission, when he noted the onset of mild aching pain in the epigastrium, constant and not accentuated or relieved by food, and without radiation. One week before admission, yellow-brown staining of the skin, sclerae and urine appeared, but the color of the stool was not noticed. Patient weighed 135 pounds 2 years ago, and on admission weighed 113 pounds, the greatest loss of weight having occurred in the month prior to admission. Generally, he felt weak and complained of some dizziness when lifting. History was otherwise negative by systems; tobacco and alcohol were used in moderation.

*Physical examination* revealed patient to be a thin, slightly built Filipino male, appearing about his stated chronologic age, deeply jaundiced, with scattered excoriations and 2 spider telangiectases on chest. The pupils were pin-point and irregular and did not react to light. Fundi were normal. Head and neck were otherwise negative. Blood pressure 100/68. There was a soft systolic blow heard loudest at the apex but no other abnormal heart findings. The lungs were clear throughout. The liver border was thought to be palpable some 2 to 4 cm. below the costal margin and not tender, but no other pathologic findings were noted. Rectal examination was negative. The extremities presented no significant findings and, with the exception of depression of the deep reflexes of the legs, neurologic examination was normal.

During the first 2 weeks of observation, the stools were observed to be light yellowish and on several occasions were negative for parasites and ova. Except for marked bile staining and a 4+ sugar reaction, repeated urinalyses were negative. Gastric analysis showed a maximum free acid of 40 and combined of 70 degrees. The blood Wassermann test was negative. The erythrocytes numbered 3,800,000 and the leukocytes 11,050 (neutrophils 65%, lymphocytes 33%, monocytes 2%, and eosinophils 2%). The hemoglobin was 70%. The sedimentation rate was 27, icterus index 159.5, and fasting blood sugar 287.8 mg. Hippuric acid liver function test yielded 0.3 gm. The bleeding time was 1 minute and the coagulation time (Lee and White) 5 minutes. Roentgen ray of the lungs was reported as showing a healed gland in the right hilar region and a healed tubercle at the right base. Gastro-intestinal series was essentially negative with the exception of slight "pattern variation" in the distribution of the barium in the colon. A flat plate of the abdomen was suggestive of an enlarged spleen but not of enlarged liver. It was found impossible to fill the gall bladder. During this period and subsequently, there was no abdominal pain. Low grade fever, not exceeding 37.6° C. was noted on several occasions.

During the period from Feb. 12, 1944, to the middle of March, 1944, the patient apparently did well. A diet containing C 230, P 85, F 45 was taken daily, and at the beginning of the period 30 units of protamine zinc insulin were given each day. On February 15, this was increased to 35 units, which dose was maintained until February 21, when 32 units were given. Successive reductions were 27 units on February 25, and 20 units on February 28. On this regimen, small amounts of sugar appeared in the urine at first, but all later specimens showed either no sugar or traces too small to be quantitatively estimated. The patient felt stronger and gained a few pounds in weight. The stool was bile-stained for the most part, but occasionally clay-colored stools were noted. The icterus index was 252 on February 18, 240 on February 23, 225 on March 1, 196 on March 10, and 192 on March 14, 1944.

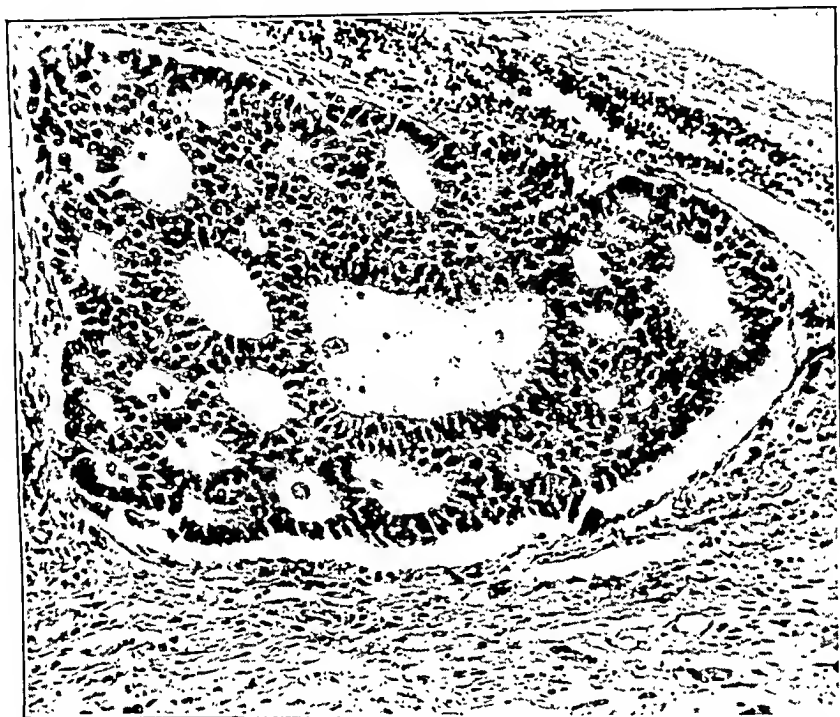


FIG. 1.—Liver showing adenocarcinoma and cirrhotic stroma. Van Gieson-Weigert iron chloride.  $\times 175$ .

From the middle of March to March 27, a small amount of edema of the legs was noted and toward the end of the period frank ascites developed. A feeling of well-being continued, however, and patient's general condition was considered fair. On one or two occasions, there was some bleeding from the gums which stopped after the administration of vitamin K for several days. The icterus index, however, again started climbing and patient's stools were noted to be clay-colored. On March 17, the icterus index was 210 and on March 25, 240. Serum protein on the latter date was 5.7 gm. On March 27, total blood cholesterol was 170, icterus index 300, and Van den Bergh immediate direct positive. The urine continued sugar-free and there was gain in weight of several additional pounds attributed to the development of ascites. Low grade fever not exceeding  $37.5^{\circ}\text{C}$ . was noted at intervals of several days.

On March 27, 1944, exploratory laparotomy was performed. On opening the abdomen, approximately 1 quart of ascitic fluid, brownish in color, was aspirated. The liver was uniformly studded with small bluish-green nodules

and generally dark. The spleen was moderately enlarged. The pancreas, common duct, stomach, and duodenum were regarded as normal. The gall

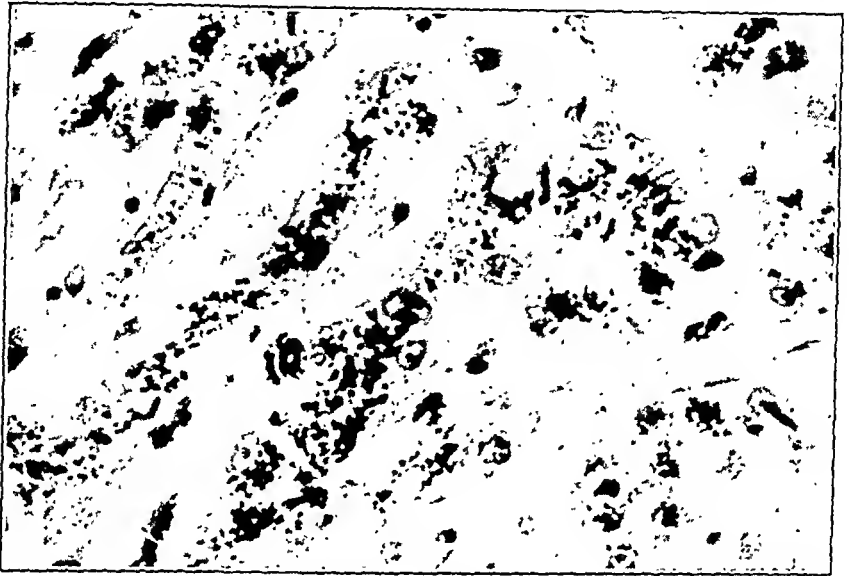


FIG. 2.—Liver showing Prussian blue reaction for hemosiderin. Note clusters of granules within the cells of the hepatic cords.  $\times 700$ .

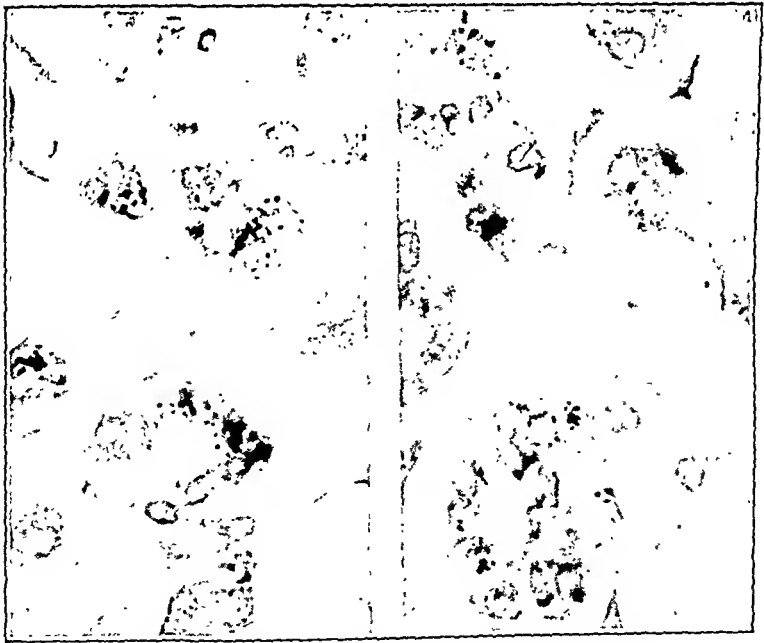


FIG. 3.—Pancreas showing Prussian blue reaction for hemosiderin. Note hemosiderin granules within the epithelial cells of acini.  $\times 1000$ .

bladder was contracted and small. Some lymph nodes were palpable retroperitoneally behind the common duct. A small wedge was taken from the anterior right lobe of the liver for histologic study.

**Liver Biopsy.** Gross. A nodular, bile-stained liver specimen roughly 1.5 cm. in diameter.

**Microscopic.** There was intense thickening of the periportal stroma accompanied by a dense infiltrate of neutrophils, plasma cells, and lymphocytes. The liver lobules were of various sizes and had lost relationship to the central veins. The hepatic cells were often enlarged, their cytoplasm frequently granular and vacuolated and in many was a large amount of granular brown pigment which, with special staining, was shown to be hemosiderin. In addition to hemosiderin many liver cells and some bile ducts contained masses of greenish-yellow pigment. A little hemosiderin was seen in the stroma.

**Diagnosis.** Hemochromatosis with associated portal cirrhosis and chronic active hepatitis.

From March 27, 1944, the patient progressively became less interested in life. During this period, although at least 200 gm. of carbohydrate were administered daily, intravenously or orally, no sugar ever appeared in the urine and blood sugar was 114 mg. Insulin intake was gradually reduced. On April 1, the dose was 16 units, on April 7, 10 units, and on April 8, 1944, the last reduction was made to 5 units. Stools during this period were completely clay-colored, the urine darkly bile-stained.

The patient became comatose 2 days before death which occurred April 10, 1944.

**Autopsy** (Dr. J. D. Gioia). The skin of the forehead and neck was bronze in color and the trunk and extremities a deep greenish-yellow. The body hair was abundant and the distribution normal. There was pitting edema of the lower back and of the ankles and feet.

**Abdomen.** The peritoneal cavity contained 2500 cc. of serosanguinous fluid. The liver edge was 5 cm. below the costal margin.

**Thorax.** The left pleural cavity contained 100 cc. of clear fluid similar to that seen in the abdomen.

**Heart.** Weight 290 gm. Appeared normal.

**Aorta.** Normal with exception of several atheromatous patches.

**Lungs.** Right 510 gm., left 760 gm. Each lower lobe was firm and non-crepitant, dark red in color and on section was homogeneous in appearance. The mid-lobe and upper lobe were moderately crepitant. On section profuse foamy golden yellow serous fluid exuded.

**Gastro-intestinal Tract.** The esophagus, stomach, and intestines appeared normal.

**Liver.** Weight 1590 gm. It appeared smaller than normal and was very firm. Surface of the left lobe was studded with blue-black nodules which range from 1 mm. to 1 cm. in diameter. The color of the tissue which formed the intervening depressions was greenish-gray. The cut section appeared similar to the external surface. Portal canals and hepatic veins were distended. The left lobe externally appeared the same as the right but sections revealed clusters of conspicuous soft, yellow nodules of from 1 to 5 mm. in diameter. The caudate lobe stood out as if a large egg were distending its capsule. On sectioning numerous discrete nodules of from 0.5 to 2 cm. in diameter were revealed. Inferiorly overlying the vena cava and encircling the hepatic and cystic ducts was a mass about 4 cm. in diameter. On sectioning this mass resembled that seen in the caudate lobe.

**Gall Bladder.** Of normal size; contained gelatinous inspissated bile.

**Spleen.** Weight 210 gm. Except for the slight increase in size, appeared normal.

**Pancreas.** Weight 120 gm. Appeared normal in size and shape; it was of firm consistency and light yellow in color.

**Kidneys.** Right 200 gm., left 180 gm. Each was bile-stained but otherwise appeared normal. The urinary bladder, prostate, and testis were bile-stained but in other respects seemed normal. Adrenals and thyroid appeared normal. The central nervous system was not examined.

**Microscopic.** *Liver.* As observed in the biopsy, there was portal cirrhosis and the same type of hemosiderin pigmentation was present in the liver cells.



There was relatively more hemosiderin in the periphery of the lobules. Some hemosiderin granules were also seen in the bile capillaries and in phagocytic cells of the stroma. Occasionally a lobule of liver cells showed very little pigment. The tumor consisted of cords and acini of large polyhedral cells with leptochromatic nuclei and granular amphophil cytoplasmic zones. The pattern was moderately uniform. Cells in mitosis were seen in small numbers. In some areas, a few tumor lumina contained mucoid material. As it was supported by the liver stroma, the tumor assumed a lobular pattern somewhat like that of the preëxisting liver.

*Pancreas.* There was a diffuse mild interstitial fibrosis. This stromal fibrosis occasionally involved an islet. There were clusters of hemosiderin pigment granules in the lining cells of many acini.

*Spleen.* There were widened sinuses and some thickening of the pulp stroma. There was considerable hemosiderin either free or in phagocytic cells.

*Kidney.* The glomerular capillaries appeared swollen and nearly filled the capsules. The proximal and distal convoluted tubules exhibited swollen and often degenerating epithelial cells. Numerous bile casts were present. An area of suppuration about 0.5 cm. in diameter was seen in a papilla.

*Skin.* In a section from the leg there were many granules of hemosiderin pigment deposited about the capillaries or glands of the corium. Specimens from the chest and shoulder were without pigment.

Breast, adrenal, testis and thyroid showed no deposition of hemosiderin; unfortunately no specimen of heart was examined. The lung showed emphysema and a terminal pyogenic bronchopneumonia. The gall bladder exhibited chronic active cholecystitis.

A quantitative analysis\* for iron yielded 50 mg. in 32 gm. of formalin fixed liver. On this basis it was estimated that the total organ contained 2.484 gm. The average iron content in human liver found by Donath,<sup>2</sup> as result of 260 autopsies, was 258.1 mg. Therefore, this liver contained an estimated 10 times the normal amount of iron.

**Discussion.** The adenocarcinoma probably arose in the intra-hepatic biliary duct system. The ensuing obstructive jaundice was an important factor in bringing about death though the tumor had involved a relatively small part of the liver and had not metastasized. The portal cirrhosis and hemosiderosis of the liver, the early diffuse fibrosis and hemosiderosis of the pancreas and the clinical diabetes appear sufficient evidence to warrant a diagnosis of hemochromatosis even though deposition of hemosiderin in the liver and pancreas was not as heavy as is usually seen in postmortem examinations of people dying of this disease. Had the tumor not caused death by biliary obstruction it is probable that the classical features of hemochromatosis would later have developed.

The iron pigmentation in the specimen of skin removed from the anterior part of the leg cannot definitely be interpreted as a disturbance in iron metabolism as this area is subject to much minor trauma and skin specimens from the shoulders and neck showed no iron. The spleen is so frequently the site of iron pigmentation that the relatively large amount of hemosiderin there is not considered to be of diagnostic value.

**Summary.** The case of a Filipino male, aged 48, who showed clinical and pathologic features of hemochromatosis complicated by obstruc-

\* The analysis for iron was made by Principal Industrial Toxicologist, L. T. Fairhall, Division of Industrial Hygiene, National Institute of Health, Bethesda, Md.

tive jaundice due to adenocarcinoma, is reported. This brings to 37 the recorded number of cases of hemochromatosis associated with primary hepatic carcinoma.

## REFERENCES

1. BERK, J. S., and LIEBER, M. M.: *AM. J. MED. SCI.*, **202**, 708, 1941.
2. DONATH, W. F.: *Mededeel. Dienst Volksgezondheid Nederlandsch. Indië*, p. 184, 3926 (III).
3. SAWARD, E. W.: *New England J. Med.*, **226**, 264, 1942.
4. WILLIS, R. A.: *Med. J. Australia*, **2**, 666, 1941.

# PROGRESS OF MEDICAL SCIENCE

## SURGERY

UNDER THE CHARGE OF

I. S. RAVDIN, B.S., M.D.\*

HARRISON PROFESSOR OF SURGERY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

AND

C. G. JOHNSTON, M.S., M.D.\*

PROFESSOR OF SURGERY, WAYNE UNIVERSITY, DETROIT, MICH.

---

## WOUNDS OF THE HEART

By M. H. BLAU, M.D.

DETROIT, MICH.

(From the Department of Surgery, Wayne University College of Medicine, and  
The Detroit Receiving Hospital)

SURGERY of the heart, while still limited in scope, is today not so unusual a procedure as it was even so short a time as 20 years ago. Consistently successful attempts to ameliorate certain chronic heart disease entities have been reported only in recent years.<sup>10,25</sup> A much longer experience has accumulated with regard to surgical intervention in cases of cardiac trauma, but even in this regard, surgery of the heart has not been practiced for long. A review by Vaughan<sup>44</sup> in 1909 reported 150 cases in which surgery had been performed on traumatic lesions of the heart. Sir Charles Ballance<sup>1</sup> presented a good review of the early concepts regarding this subject.

In 1687, Barbette<sup>2</sup> of Amsterdam stated that wounds of the heart are always mortal and those that penetrate into the left ventricle kill suddenly. Those so wounded seldom live 12 to 20 hours, although occasionally one finds an example to the contrary. Tourby,<sup>41</sup> in 1642, did an autopsy on a man who 4 years previous had had a sword thrust in the chest which caused a wound in the heart near the apex; the evidence of which was a cicatrix that could be easily demonstrated.

In the centuries to follow there is little to note until the eighteenth, when Bonetus,<sup>9</sup> in 1700, and Morgagni,<sup>34</sup> in 1730, established the facts that a sudden filling of the pericardial sac arrested the heart's action and that wounds of the heart were not necessarily immediately fatal. Bonetus<sup>9</sup> relates the case of a young man, age 24, who bravely sustained an attack by 7 others and was at length wounded by a sword thrust. He survived 5 days. The wound was of the left lung and of the right ventricle of the heart.

Morgagni<sup>34</sup> notes two types of heart wounds. In one there was an opening in the pleura as well as the pericardium and the blood escaped freely into the pleural space. Likewise, blood escaped freely externally. In 1 case,

\* Now on Active Service in the Armed Forces.

with external bleeding, the patient survived 8 days; in another case the blood was retained in the pericardial sac and the patient died within a few minutes. He points out that the second case did not die from hemorrhage but from pressure on the heart. Thus, as pointed out by Morgagni, a hemorrhage within the pericardial sac, in spite of the small amount of blood lost, may be quickly fatal.

In the early nineteenth century many surgeons regarded operative procedures on the heart as hopeless. Dupuytren<sup>20</sup> advised venesection to be carried out almost to the point of exsanguination as a treatment for wounds of the heart. Guthrie<sup>26a</sup> in 1848 stated that in all of London with its 2 million inhabitants there was not a surgeon who had seen or recalled a case of recovery after a wound of the heart. At a later date, commenting on the surgery of warfare in Portugal, Spain and France, Guthrie<sup>26b</sup> in 1855 writes "that the heart when wounded is capable of recovery by the permanent closure of the wound, in a few rare instances, is indisputable; and it would seem, from a consideration of the different cases which have been recorded, that such recovery takes place in consequence of there being but little blood discharged through the wound, or into the pericardial cavity, or into that of the pleura. The absence or the cessation of the hemorrhage by the contraction of the wound, or the formation of a coagulum, is the first step toward a cure. . . . If all the circumstances be considered, there can be no doubt of the propriety of closing the wound in the first instance, if the flow of blood be excessive and appears likely to endanger life. . . . When the sufferer has recovered from the imminent danger attendant on the infliction of the injury, and the pericardium is believed to be so full of blood as to prevent in a great measure the movements of the heart, it has been proposed by Baron Larrey to open the pericardium."

Early experimental studies on the heart revealed many important observations. One of these by Morgagni<sup>34</sup> in his *De Sedibus et Causis Morborum*, in 1761, showed that a puncture of a coronary artery might cause a hemorrhage into the pericardial sac and so compress and arrest the heart. In 1882, Block<sup>8</sup> sutured heart wounds in rabbits. In 1895, Del Vecchio<sup>18</sup> made a wound in the heart of a dog and successfully sutured the wound. Following this successful operative procedure, he suggested that the method should be adopted in operations on man. Thus experimental evidence indicated that a wound in the cavity of the ventricle could be successfully sutured and that blood effused into the pericardium would embarrass the action of the heart unless it was removed. In 1919, Warbasse<sup>45</sup> following experiments on dogs suggested that the apex of the heart be pulled forward by a fixation stitch to control the bleeding by compressing the great vessels at the base, keeping the heart empty and the operation relatively bloodless.

Suture of the heart in the human was carried out by Cappelen<sup>11</sup> by Farina<sup>23</sup> of Rome, and by Rehn<sup>37</sup> of Frankfurt in 1896. The cases of Cappelen and Farina died 2½ and 5 days after operation respectively. Rehn's case was recovering well on the 14th day. A description of their cases follows: Cappelen's case was a man, age 24, who was stabbed in the fourth left interspace in the mid-axillary line. He went home following the stab wound and about 1 hour afterwards was found lying in a pool of blood. He was unconscious and pulseless but his heart sounds were audible. At operation the pericardium was found distended with 1400 cc. of blood. The 1 cm. wound in the pericardium was enlarged and a 2 cm. wound was found in the ventricle. The wound was

sutured and a bleeding artery on the heart tied. The patient lived  $2\frac{1}{2}$  days, dying of septic pericarditis.

Farina's case was a man, 30 years of age, who received a blow from a fine, sharp dagger in the left fifth intercostal space in the parasternal line. The wound in the ventricle was oblique, from above downward and 7 mm. long. The wound was repaired with interrupted silk sutures. On the 5th postoperative day the patient developed pneumonia and died 3 days later. At autopsy the heart wound was found healed.

In Rehn's case, the patient was stabbed in the left chest with a table knife. He exhibited signs and symptoms of tamponade. On the following day, Rehn relieved the tamponade and sutured the lacerated heart. On the 14th postoperative day the patient was in good condition.

The first case of gunshot wound of the heart with an attempted repair as recorded by Vaughan<sup>44</sup> is that by Marion in 1898. This was a through and through perforation of the right ventricle from a pistol ball. The anterior wound of the heart was sutured but the patient died on the operating table. The first successful repair of a gunshot wound of the heart, according to Vaughan,<sup>44</sup> is recorded by Launay in 1902. In his case the left ventricle had a through and through perforation. Both perforations were closed, drains were placed in the pericardium and the pleura and the patient recovered.

Since the turn of the century there have been many successful cases reported in which the injured heart was repaired. Despite advances in surgery the mortality from wounds of the heart is as expected, quite high. The following series of statistics on penetrating wounds of the heart indicate the seriousness of such cases.

<i>Author</i>	<i>Year</i>	<i>No. of cases</i>	<i>Mortality</i>
Vaughan <sup>44</sup> . . . .	1909	150	65.0
Touffier <sup>40</sup> . . . .	1920	350	49.7
Cutler <sup>17</sup> . . . .	1932	28	22.4
Bigger <sup>4</sup> . . . .	1932	53	26.5
Bigger <sup>5*</sup> . . . .	1939	141	50.0

\* Report by Bigger includes cases from members of American Association for Thoracic Surgery, American Surgical Association, and Southern Surgical Association.

In our own series of cases from the Detroit Receiving Hospital there were 27 cases of penetrating wounds of the heart, 21 cases were operated upon, 16 lived, a mortality of 23.8%. In addition, there were 6 cases, 3 of which were simply observed, and aspiration of the pericardium was performed in 3 others. The mortality in this group was 6%. Of the entire group of 27 cases cared for from 1939 to 1944, the mortality was 22.2%; there being 21 cases which lived, and 6 died. Of the injuries, 25 were stab wounds by knives or ice-picks; the remaining 2 were gunshot wounds.

**Pathologic Physiology.** The filling of the heart depends on the fact that the pressure within the great veins is slightly higher than that in the right auricle during diastole; the greater the pressure within the large veins the more rapidly will the blood enter the heart. The filling of the right auricle may be impeded by anything which hinders the expansion of the heart, such as the presence of fluid in the pericardial cavity. This can be shown experimentally, or as a result of fluid in the pericardial sac. Increasing the pressure within the pericardium and thus interfering with the venous return increases the pressure in the vena cava. Owing to the resistance offered by the pericardium, which is a tough fibrous inextensible

sac, the increase in venous pressure may be unable to force blood into the heart. When the pressure of the fluid in the pericardial cavity is sufficient to prevent blood from entering the heart, death ensues.

The effect of penetrating wounds of the heart varies with the size of the wound, its character, direction, heart chamber involved, associated coronary artery involvement, and area of confinement of the blood. Simple myocardial wounds or lacerations of the coronary vessels may cause death by direct hemorrhage producing heart compression in the closed pericardium. When larger branches of the coronary arteries are involved in the trauma, secondary myocardial infarction may be expected. Wounds of the auricles are considered more dangerous because of continued bleeding, as the auricles are thin-walled and possess less power of contractility. Wounds of the ventricles are less dangerous, especially the left. The thickness of the ventricular wall and the columnæ carneæ favors thrombus formation.

In wounds of the heart, as in other vascular injuries, hemostasis is frequently obtained by the formation of a thrombus which may plug the wound for a variable time after the injury. As arterial pressure increases, the clot may be released by the slightest exertion and thus death may occur a few days after the patient is apparently doing well. It has been shown clinically<sup>1,31a</sup> that especially in the ventricles, the thrombus remains and organizes, as a rule, leaving a relatively thin cicatrix in the region of the epicardial opening. The remaining part of the wound tract, instead of healing may persist as an open space connected with the heart chambers and lined by endothelium. Thus a false sacculated cardiac aneurysm may occur.

Sir George Henry Makins,<sup>30</sup> in 1920, in reviewing specimens of penetrating wounds of the heart noted in some that there was little evidence of hemorrhage into the pericardial sac. In these instances the wound in the wall of the heart became closed by thrombus formation. Constantini and Mocquot<sup>14</sup> refer in particular to delayed symptoms in 11 cases of wounds of the left ventricle. In these cases hemopericardium occurred some time after injury.

Vance,<sup>43</sup> in 1925, refers to 2 cases which at autopsy showed that healing may occur without operative interference. In his first case a bullet had cut a tunnel in a segment of heart muscle with little bleeding, death being due to pneumonia and spinal cord injury. In the second case, the heart and aorta were penetrated by a small bullet, the patient experiencing no trouble until 8 days afterward when the edges of the wound in the heart were suddenly forced apart and death resulted from tamponade.

Long,<sup>28</sup> in 1925, discussed at some length the mechanism of the production of tamponade. The possible mechanisms of closure of the parietal pericardial opening which prevents blood from escaping are: "(1) A clot which is effective only when the blood pressure has fallen very low as a result of shock or hemorrhage. (2) Displacement of the myocardial opening so that it does not coincide with that in the pericardial. This occurs somewhat at each heart beat, and as hemopericardium is increased, the relation of the openings is further changed because the blood collects in the lateral and posterior recesses, thus crowding the heart forward against the anterior portion of the sac. The greater the pressure behind the heart, and the less complete the diastole and systole, the more completely is the pericardial opening occluded; if it is in the anterior portion of the sac. (3) A small puncture of the pericardium may accompany an extensive myocardial opening, as, for example, impalement by a batpin, upon which

the heart, by its own contractions, tears itself. (4) Heart tamponade is relatively more common and develops more rapidly in those cases in which neither pleural cavity is opened. The usual sliding of tissues obstructs the outlet." If an opening in the pericardium is large and it connects with the pleural cavity, tamponade will not occur. The patient will exhibit signs of hemorrhage and will have blood in the pleural cavity.

Cohnheim,<sup>13</sup> in 1881, stated that the ligation of one of the coronary arteries induced immediate and fatal arrest of the heart in the dog. That this is incorrect is well borne out by clinical and experimental data. Porter,<sup>36</sup> in his exhaustive research on dogs, showed that the fatal result in coronary artery ligation depended on the size of the artery. He performed a series of ligations on dogs; arrest never being observed after ligation of the septal branch alone; rarely observed (14%) with the right coronary artery; more frequently (28%) with the descending branch of the left coronary; and with the greatest frequency (64%) if the circumflex branch of the left coronary was ligated. It is also evident that the resulting disturbances are less dangerous if these vessels are ligated at a distance from their origin. These factors can only be accounted for by the presence of a collateral circulation. Elkin<sup>22</sup> had a case with severed coronary artery and the patient recovered. Electrocardiographic evidence of coronary occlusion did not appear until 36 hours after the accident.

**Classification of Heart Wounds.** The following classification of wounds of the heart is a modification of that presented by Bigger<sup>5</sup> and Mayer.<sup>32</sup>

Heart wounds may be classified into four groups:

*Group I.* Cases with gunshot and other large perforating wounds which produce severe injury.

*Group II.* Cases with a lacerated epicardium only or a lacerated epicardium plus an incomplete laceration of the myocardium.

*Group III.* Cases in which the missile has entered the chambers of the heart or a coronary vessel has been lacerated.

*Group IV.* Cases with a pericardiopleural communication.

**Symptomatology and Physical Findings.** In Group I the injury is usually so severe that death occurs before surgical aid can be given.

In Groups II and III the findings and symptoms are variable, depending upon the amount of bleeding and the rapidity with which tamponade occurs. Many of these cases show satisfactory progress without surgical intervention other than aspiration of the pericardial sac.

The only physical signs which provide a definite diagnosis are those of heart tamponade. The presence and position of the wound are usually such as to suggest cardiac injury. In tamponade, the circulatory collapse is out of proportion to the blood loss. There is respiratory distress and pallor with cyanosis. The blood pressure is usually low and may not be obtainable, but if it can be measured, the pulse pressure is apt to be lower than is found even in the case of massive hemorrhage. Early the pulse rate is slow, but when tamponade persists for several hours, the pulse rate increases. Physical findings over the pericardium such as increased dullness and distant heart sounds, as well as venous stasis with distention in the neck and arm veins, is an aid in the diagnosis. The presence of a water bottle contour to the heart shadow with diminution of the action of the heart as noted by fluoroscopy tends to confirm the diagnosis of tamponade.

In Group IV, with the pericardiopleural communication, there is a constant leakage of blood into the pleural cavity. The patient usually shows evidence of shock from marked hemorrhage. There is pallor without

cyanosis. The pulse is soft and rapid, and the blood pressure may be low or absent. There is profuse sweating and the body is cool. Consciousness is usually lost. It is in this group of cases that the diagnosis is frequently most difficult to make.

**Treatment.** In 1868, Fischer<sup>24</sup> collected from the literature a series of 452 cases of wounds of the heart with a mortality of 85%. The treatment employed at that time was rest, venesection, application of leeches, and occasionally, when possible, the passage of a catheter or sound into the wound for evacuation of fluid from the pericardial cavity.

In 1894, Del Vecchio<sup>28</sup> following experimental work on dogs doubted the necessity for operative interference in the treatment of tamponade. He states, "death in cases of wounds of the heart seems to be chiefly due to pressure from the blood effused into the pericardial sac. Since this pressure is also a check to further hemorrhage, it is a doubtful question whether operative interference may not do more harm than good as far as the hemorrhage is concerned. Paracentesis may, however, be practiced to be followed if necessary by free incision of the pericardium."

In 1928, Cox<sup>25</sup> used a needle successfully to aspirate the pericardial sac following the reaccumulation of fluid postoperatively. In 1933, Singleton<sup>29</sup> discussed a case in which 250 cc. of fluid was aspirated, and states, "following this the patient which had been moribund became tranquil, felt comfortable and the circulation returned to normal. Without prompt relief from aspiration the patient would have died from heart compression." Beekman<sup>3</sup> in the same year aspirated 100 cc. of blood and relieved the tamponade immediately; 9 hours later, however, the tamponade recurred and the patient was operated upon and recovered.

From the above it is obvious that every person with cardiac tamponade need not be operated upon, as also stated by Blalock,<sup>7</sup> and by Graham, Bigger, Churchill and Eloesser.<sup>42</sup> This operation becomes imperative if tamponade persists. The aspiration of blood from the pericardial sac may be a life-saving procedure to reduce intrapericardial pressure temporarily in those cases in which the patient has not been seen until a marked degree of cardiac tamponade has developed. Time may be obtained to make such preparations as are necessary for surgical intervention and the patient's condition improved by aspiration. The fact that Fischer,<sup>24</sup> in 1868, reported an 85% mortality, and McGuire and McGrath<sup>29</sup> as late as 1937 a mortality of 82% in cases not operated upon, does not presuppose that conservative therapy is contraindicated in cases with tamponade when associated with watchful waiting and aspiration of the pericardial sac.

In those cases with persistent bleeding and with pericardiopleural communication, operative intervention becomes imperative. In those cases with resulting tamponade, the blood should be aspirated from the pericardium by the costo-xyphoid route. If there is a recurrence of tamponade then exploration and cardiorrhaphy should be performed. Pericardiocentesis is an important adjunct in the treatment of cardiac wounds where tamponade is present. This simple form of therapy has too often been neglected.

According to Blalock,<sup>6</sup> if intravenous fluids are given when tamponade is present, the blood pressure is not increased and the patient is not appreciably improved. From our experience in patients with tamponade, if blood is forced into the veins rapidly there is temporary improvement in the blood pressure.



*Choice of an Anesthetic.* Either local or inhalation anesthesia can be used for repair of heart wounds. Local anesthesia is more time-consuming. In addition, in patients who are alcoholic or uncoöperative, the operation is associated with greater difficulty under local anesthesia. Frequently when the pleural cavity is opened, the difficulty in controlling mediastinal shift and collapse of the lung is so great that successful continuation of the operation is impossible. In inhalation anesthesia the procedure can be carried out with more efficiency and increased rapidity, and in cases where the pleura is opened, positive pressure anesthesia is a great aid. Operation on a moribund patient without anesthesia should not be attempted as has been suggested. The same principles should pertain in cardiac injuries as in other acute surgical conditions. In the case of a moribund patient with tamponade, aspiration of the pericardial sac will decrease the surgical risk, and in cases where there has been marked blood loss, restoration of blood volume by transfusion is important.

*The Operative Treatment of Cardiac Wounds.* The techniques for operative approaches to the heart are many. Variation in the approach will depend on the pathology involved. In this paper we wish to include only a brief résumé of methods as related to the approach and repair of cardiac wounds. More comprehensive surveys are to be found in articles by Cutler and Beek,<sup>16</sup> Matas,<sup>31</sup> and Shipley.<sup>38</sup>

Of the various methods, two types suffice:

1. Parasternal incisions: These incisions are usually on the left side and may or may not enter the pleural cavity. They are grouped by Matas<sup>31</sup> as follows:

(a) Simple intercostal incisions which do not involve the bony thorax and include only the soft parts.

(b) Thoracotomy with excision of the costal cartilages and ribs.

(c) Osteoplastic flaps which contain sections of both cartilages and ribs. These flaps may be in any direction and contain either the entire thickness of the wall *en masse*, or in layers.

2. Median thoraco-abdominal incision of Duval-Barastý,<sup>21</sup> as used by Milton,<sup>33</sup> and Beck.<sup>16</sup> The median incision not only exposes the heart completely, but also protects the pleural cavities. However, in traumatic wounds where time is usually an important factor, the median incision will be found to be time-consuming.

The parasternal incision we have used in our cases, whether transpleural or extrapleural, is as follows: A horse-shoe shaped incision is made over the left chest extending along the course of the third rib from the nipple line to the sternal margin. The incision is then carried along the left sternal margin to the fifth costal cartilage where it again extends to the nipple line over the fifth rib. The skin and pectoralis muscles are brought up in one flap exposing the costal cartilage and portions of the ribs. The costal cartilages of the third, fourth and fifth ribs, as well as portions of these ribs are removed, leaving the periosteum and perichondrium behind. If the pleura was previously opened by the stab wound, it is further incised exposing the pericardial sac. If the pleura is intact, it is gently pushed away from the pericardial sac, thereby eliminating the danger of injury to the pleura during the operation.

In most of our cases the heart has been exposed through a transpleural approach, under positive pressure anesthesia. This incision has allowed ample room for suture of the injuries to the left auricle and ventricle and in most cases of the right ventricle. In one instance, with a gunshot wound of the right auricle, a right parasternal incision was used.

Many transpleural approaches were formerly discredited because of the risks and danger of the sudden admission of air into the pleural cavity. The use of positive pressure insufflation has diminished the operative risk. When the pleura is not involved, and there is no pneumothorax, opening the pleural cavity increases the operative risk moderately and should be avoided if possible.

The pericardial sac, which has been thus exposed, is opened and the blood evacuated. There was little or no bleeding from the heart wound at operation in several of our cases when the ventricle alone had been perforated. Interrupted sutures of silk were used to seal the wounds, the long ends of the suture being gently used to steady the heart. The "control suture" in the apex as used by Warbasse<sup>45</sup> in his experiments on dogs and more recently by Cutler and Beck<sup>16</sup> were also used in a number of our cases. It should be pointed out, however, that if too great a traction is used on the control suture there will result persistent, even though slight, bleeding.

In those cases in which a large defect in the heart is seen through the pericardial sac, the pericardium can be utilized to plug the opening and prevent the intermittent gushing of blood from the wound. The pericardium can then be incised a short distance from the control pressure point and the wound sutured.

*Pericardiocentesis* has been performed for some time for diagnosis of pericardial effusion as well as for decompression in infectious processes. It has likewise been used in hemopericardium from traumatic heart wounds. Matas<sup>31c</sup> referred to this procedure as a form of treatment of traumatic wounds of the heart with hemopericardium. This form of treatment has not been used as frequently as it should for fear of wounding the heart or coronary vessels with serious consequences. In the interest of obviating such dangers, many and varied types of needles or trocars have been devised. The site chosen for the introduction of the exploring needle should not injure the mammary vessels, pleura or the heart and at the same time provide a certainty of reaching the large collection of fluid in the most favorable position for aspiration. Numerous sites have been advised for this procedure. There are two sites we prefer for doing a paracentesis. In the xiphoid approach the needle enters the left xiphoid space at its extreme upper edge of the chondro-xiphoid angle. This offers greater advantages and less risk than any other method. The needle is driven obliquely upward and backward at this point so as to avoid the diaphragm and enter the pericardial sac without touching the pleura or peritoneum. In the other approach we have used, the needle is inserted into the sixth left intercostal space, close to the margin of the sternum. When inserting the needle in either method, a gentle vacuum in the syringe should always be present and the patient's bed rest be in a semirecumbent position. The inability to aspirate fluid in the pericardial sac does not necessarily exclude the presence of fluid, as blood clots may be present to block the needle or the needle may not have been inserted properly.

Inasmuch as a high mortality and morbidity still exist in the care of cardiac wounds with tamponade, it becomes apparent that any procedure which can reduce this mortality should be given wider use. This is especially true when slender knives, or ice picks are the causative agents. These wounds are usually 1 to 2.5 cm. in length and most often enter in an oblique direction through the heart musculature. These wounds have a tendency to seal off early with thrombus formation. This is possible when the blood accumulating in the pericardial sac compresses the wall

in the region of the wound and prevents continued bleeding. This has been a frequent observation in the cases we have explored. Following release of the tamponade during the operation, the heart was carefully examined and frequently the wound was not found until by digital manipulation the wound edges separated and some bleeding occurred. We have also observed early thrombus formation at postmortem in one of our cases under observation in which there was no tamponade present. In another case, where a bullet tunnelled the musculature of the heart, no bleeding was evident when the tamponade was released. From these observations it becomes evident that before any operative procedure is contemplated the pericardial sac should first be emptied and the patient watched for reaccumulation of fluid. It is necessary to keep these patients quiet for a few days in order to prevent the release of the early thrombus when under exertion. However, when a large object, such as a bullet, piece of shrapnel, or a wide butcher knife is the causative agent, operation will probably be the only life-saving procedure, and aspiration should be utilized to get the patient in better condition and to allow time for preparation for the operation.

In our last 3 cases of stab wound of the heart with tamponade, aspiration was the only treatment necessary. Only one aspiration was necessary and all 3 patients responded nicely.

*Immediate Postoperative Complications From Heart Wounds.* The postoperative complications either immediate or late may include any of the following: Coronary occlusion, pericarditis, pericardial effusion with tamponade, thrombosis with secondary emboli, ventricular fibrillation, hemothorax, hemopneumothorax, tension-pneumothorax, empyema, pneumonia, atelectasis, and bacillus gas infection.

The most important complications postoperatively in cases of cardiorrhaphy are infection and reaccumulation of fluid in the pericardial or pleural sac. If an opening is not left in the pericardium at the time of the operation, any fluid which may accumulate will not have an opportunity for exit into the pleural cavity or out through the external wound. Effusion into the pericardium is inevitable after an operative procedure on the heart and postoperative tamponade may occur if the pericardium is closed too tightly. While a drain in the pericardium may obviate this, the presence of a drain does more harm than good and should not be used.

In our experience the most frequent complications have been atelectasis and hydrothorax. We have had no cases with postoperative cardiac tamponade where the transpleural approach was used. With the pericardial sac loosely closed any drainage that takes place in the pericardial sac can escape freely into the pleural cavity. We have no cases with serious postoperative infection. Atelectasis ought to be watched for and treated early. In our series, bronchoscopic aspiration has been necessary in but 2 instances. Hemothorax and hydrothorax have been our most common postoperative complications. This has caused no serious trouble as we have resorted to aspiration of the fluid when necessary.

*Late Postoperative Outlook.* In 1925, Dshanelidze<sup>19</sup> collected 535 cases (1896 to 1921) of cardiac trauma and analyzed the late postoperative results. Operations had been done for a stab wound in 402 cases, and for projectile injuries in 133. The immediate mortality was 56 %. In 96.5 % of 113 cases traced for 2 months up to 18 years, the function of the heart did not seem to be impaired. Even prolonged complicating infection did not prevent satisfactory return of function. The location of the wound and operative technique seemed immaterial. The sutured heart passed

through infectious diseases, abuse of alcohol and tobacco, long operations and the strain of childbearing. The unfavorable outcome in 3.5% was due to aneurysm and adhesions.

Cecchini,<sup>12</sup> in 1925, discussed the follow-up study of 2 patients after a period of many years had elapsed since operation. One patient was re-examined by Cecchini who had had a stab wound of the heart sutured 17 years before, and no evidence of cardiac impairment was found. He had received a report of good health from a similar second patient.

Hesse,<sup>27</sup> in 1925, compared 12 cases which he had followed for long periods after suture of the heart with 107 collected from the literature. The interval since the operative procedure ranged from 2 months to 18 years. The earning capacity was unimpaired in 80.1% and only 1.7% were disabled. The ultimate outcome was excellent and the general condition good even in 9 patients who had had purulent pericarditis.

Noth,<sup>35</sup> of the Department of Medicine of Wayne University, has followed 8 of our cases over a period of from 5 to 36 months. Five complained of a variety of indefinite symptoms and 3 had no symptoms referable to the heart. However, the latter all had abnormal electrocardiograms, whereas 3 of the 5 patients with symptoms had normal tracings. Abnormal physical findings with reference to the heart were absent except in 1 patient with complicating hypertension and syphilis and in another who had a widely split first heart sound which coincided with prolongation of the P-R interval. No patient showed retraction of the ribs. Pulsus paradoxus was specifically noted as absent in 4 patients. Venous pressure was normal in the 7 patients examined in this regard.

It is remarkable that patients who have suffered severe cardiac wounds have so few sequelæ after recovery from their operative procedure. As a rule they are able to carry on their usual work with no impairment and from this standpoint repair of the injured heart gives very gratifying results.

#### REFERENCES

- (1.) Ballance, Sir C.: Bradshaw Lecture on the Surgery of the Heart, *Lancet*, 1, 1, 73, 134, 1920. (2.) Barbette, P.: *Surgical Works*, Dernière Ed., Lyon and Paris, p. 201, 1687; cited by Sir Charles Ballance.<sup>1</sup> (3.) Beekman, F.: *Arch. Surg.*, 26, 510, 1933. (4.) Bigger, I. A.: *South. Med. J.*, 25, 785, 1932. (5.) Bigger, I. A.: *J. Thorac. Surg.*, 8, 239, 1939. (6.) Blalock, A.: *Ann. Surg.*, 93, 1278, 1931. (7.) Blalock, A., and Ravitch, M. M.: *Surgery*, 14, 157, 1943. (8.) Block: *Verhandl. d. deutsch. Gesellsch. f. Chir.*, 11 Congr., Berlin, Part 1, p. 108, 1882. (9.) Bonetus: *Sepulcretum Lib. N. Add., Obs.*, 3, 1700; cited by Sir Charles Ballance.<sup>1</sup> (10.) Bullock, L. T., Jones, J. C., and Dolley, F. S.: *J. Pediatr.*, 15, 786, 1939. (11.) Cappelen: *Norsk Mag. f. Lægevid.*; *Abstr.*, *Brit. Med. J.*, Epitome, p. 81, 1896. (12.) Cecchini, E.: *Policlinico (Sez. prat.)*, 32, 699, 1925; *Abstr.*, *J. Am. Med. Assn.*, 85, 230, 1925. (13.) Cohnheim, J., and Schultess-Rechberg, A.: *Arch. f. path. Anat.*, 85, 514, 1881. (14.) Constantini, H., and Mocquot, P.: *Rev. de chir.*, 58, 257, 1920; *Abstr.*, *J. Am. Med. Assn.*, 75, 772, 1920. (15.) Cox, D. M.: *Arch. Surg.*, 17, 484, 1928. (16.) Cutler, E. C., and Beck, C. S.: *Surg., Gynec. and Obst.*, 45, 74, 1927. (17.) Cutler, E. C.: *Surg., Gynec. and Obst.*, 54, 274, 1932. (18.) Del Vecchio: *Sutura del Cuore*, *Rif. med.*, p. 79, 1895; *Abstr.*, *Brit. Med. J.*, Epitome, p. 86, 1895. (19.) Dshanelidze, J. J.: *Arch. f. klin. Chir.*, 132, 528, 1924. (20.) Dupuytren, G.: *Clinical Lecture on Surgery*, delivered during Sessions of 1834 at the Hotel Dieu, Paris, *Lancet*, 1, 773, 1834-35. (21.) Duval-Barasty: *Presse méd.*, 1918. (22.) Elkin, D. C., and Phillips, H. S.: *J. Thorac. Surg.*, 1, 113, 1931. (23.) Farina, G.: Letter to Sir John Bland Sutton, *Brit. Med. J.*, p. 1273, 1910. (24.) Fischer, G.: *Arch. f. klin. Chir.*, 9, 571, 1868. (25.) Gross, R. E., and Hubbard, J. P.: *J. Am. Med. Assn.*, 112, 729, 1939. (26.) Guthrie, G. J.: (a) *Lectures on Some of the Most Important Points in Surgery*, Part III, p. 50, 1848; cited by Sir Charles Ballance.<sup>1</sup> (b) *Commentaries on the Surgery of the War in Portugal, Spain, France, and the Netherlands*, 6th ed., Phila., Lippincott, p. 468, 1862. (27.) Hesse, E.: *Deutsch. Ztschr. f. Chir.*, 190, 239, 1925; *Abstr.*, *J. Am. Med. Assn.*, 85, 156, 1925. (28.) Long, J. H.: *Boston Med. and Surg. J.*, 193, 1197, 1925. (29.) McGuire, J., and McGrath, E. J.:

Trans. Assn. Am. Phys., 56, 194, 1941. (30.) Makins, Sir G. H.: Brit. J. Surg., 8, 121, 1920. (31.) Matas, R.: Surgery, Its Principles and Practice, ed. by W. W. Keen and J. C. DaCosta, vol. 5, 1909; (a) p. 50, (b) p. 59, (c) p. 44. (32.) Mayer, J. M.: Surg., Gynec. and Obst., 62, 852, 1936. (33.) Milton, H.: Lancet 1, 872, 1897. (34.) Morgagni, J. B.: Seats and Causes of Disease, vol. 3, bk. 4, Exp. 63 (4 and 5) and Exp. 53 (4), 1761; cited by Sir Charles Ballance.<sup>1</sup> (35.) Noth, P.: Personal communication, Wayne Univ. College of Medicine. (36.) Porter, W. T.: American Text Book of Physiology, ed. by W. H. Howell, Phila., Saunders, p. 473, 1896. (37.) Rehn, E.: Centralbl. f. Chir., 23, 1048, 1896. (38.) Shipley, A. M.: Surg., Gynec. and Obst., 54, 280, 1932. (39.) Singleton, A. O.: Am. J. Surg., 20, 515, 1933. (40.) Touffier, T.: La chirurgie du Cœur, Cinquieme Congrès de la Soc. Internat. de Chir., Paris, Brussels, Hayez, p. 43, 1920. (41.) Tourby: Jamain des Plaies du Cœur, Thèse de Paris, 1857; cited by Sir Charles Ballance.<sup>1</sup> (42.) Graham, E. A., Bigger, I. A., Churchill, E. D., and Eloesser, L., in U. S. War Department: Guides to therapy for medical officers, Technical Manual 8-210, Washington, D. C., p. 23, 1942. (43.) Vance, B. M.: Am. J. Med. Sci., 169, 872, 1925. (44.) Vaughan, G. T.: J. Am. Med. Assn., 52, 429, 1909. (45.) Warbasse, J. P.: Surgical Treatment, Phila., Saunders, 2, 427, 1919.

## OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.

HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.

AND

H. P. WAGENER, M.D.

ASSISTANT PROFESSOR OF OPHTHALMOLOGY, MAYO FOUNDATION, ROCHESTER, MINN.

### DRUSEN (HYALINE BODIES) OF THE OPTIC DISK

By H. P. WAGENER, M.D.

For many years, in fact until very recently, "drusen" of the optic disk, also spoken of as hyaline bodies, colloid bodies, hyaline varicosities, granular formations, globular masses and kalkdrusen, have been regarded essentially as ophthalmoscopic curiosities. In the earlier days, when ophthalmoscopic examinations were less frequently made without some definite indication of visual or ocular disturbances, drusen, when observed, were usually regarded as a part or residual of the intraocular or optic nerve disturbance which was responsible for the loss of vision. As ophthalmoscopic studies became more universal in patients presenting themselves only for the correction of refractive errors or for general systemic and neurologic disorders, it became apparent that drusen were present at times in the optic disks of apparently healthy individuals without other recognizable intraocular disease. It seemed logical to assume then that the drusen were congenital structural anomalies without significance with respect to the diagnosis of systemic disease or to the future vision of the individual. Soon, it became obvious that in certain cases the drusen could produce or at least be associated with defects in the field of vision, and that these visual field defects might be progressive, possibly as the result of an increase in the number or size of the drusen. However, it was not until the publication of a paper by Reese<sup>13</sup> in 1940 that a possible systemic significance of the drusen was suggested.

Ophthalmoscopically, drusen appear usually as rounded, waxy, rather shiny or glistening, more or less translucent bodies or nodules of varying size in the substance of the optic disk. They are most or best visible as a rule near the margins of the disk and at times may seem to lie in the disk

rings or in the marginal retina or at least to overlap the margins of the disk. They are variously described as resembling frogs' eggs or tapioca grains or as mulberry-like or grape-like clusters. If numerous, they seem to impart a yellowish waxy color to the entire disk simulating that of secondary optic atrophy. This is particularly true if they lie near or on the surface of the disk. In the latter case they appear as nodular masses which may project into the vitreous; it is said as much as 14 diopters. If the drusen lie deeper within the substance of the papilla, they may cause an appearance of hyperemia or congestion of the disk with fulness and marginal blurring, and at times measurable elevation. Since such deep lying drusen are often hard to see, the diagnosis of choked disk or optic neuritis may be suggested at the initial examination. When the drusen lie mainly or extensively in the edges of the disks and overlap the marginal zones of the retina, the appearance may simulate that of peripapillary choroidal atrophy or choroiditis. Some of these various appearances have been illustrated recently in fundus photographs such as those in the articles by Reese<sup>13</sup> and by Rucker.<sup>14</sup> Rucker calls attention particularly to the field defects which have been noted from time to time by different authors as associated with drusen and probably caused by the pressure of the hyaline deposits on the nerve fibers. According to Rucker, the most characteristic field defects are enlargements of the physiologic blind spot, arcuate scotomas which may break through to the periphery or may be double and produce ring scotomas, and contractions of the peripheral fields, especially in the lower nasal quadrant. Drusen are usually bilateral but they can be or at least appear to be unilateral, since they may be very numerous in one disk and very scanty or essentially invisible in the other disk. Drusen can be observed at any age, the youngest reported case being 8 years old according to Duke-Elder,<sup>3</sup> who states, however, that they "are more common in the aged and in the presence of retinal disease." It is perhaps more generally thought now that drusen are primarily congenital formations though they can increase in size and number during the course of years.

According to Duke-Elder,<sup>3</sup> "pathologically these bodies are made up of concentric laminations with no cellular structure or capsule, and frequently showing masses of calcification. The great majority of observers agree that their basis is a hyalin-like material . . . They are associated with no surrounding inflammatory reaction." These were essentially the findings of de Schweinitz<sup>15</sup> who reported one of the relatively few cases in which microscopic examination was made of clinically observed drusen. He described the drusen as "compound hyaline bodies," oval masses of whitish color composed of a series of smaller bodies in which the markings with concentric lines was very distinct. He thought that the masses were probably cross-cuts of a ring of hyaline tissue with some calcareous deposits occupying the substance of the nerve head in advance of the lamina cribrosa, surrounding the central vessels, and not passing beyond the outer margin of the papilla. The optic nerve showed well-marked atrophy; but de Schweinitz did not think that this was connected with the drusen formation.

Goldstein and Givner,<sup>6</sup> in 1933, found drusen of the optic disk in one eye of a patient who had chronic glomerulonephritis and died in uremia. Retinopathy was present and also some atypical pigmentary deposits in the retina. Microscopically, the drusen appeared as a mass composed of concentrically arranged layers having no cellular structure or capsule. There was a definite central area of calcification and around its projecting

surface was a proliferating glial membrane which separated it from the surrounding retina and choroid. In this membrane were several discrete smaller masses of calcification. There were no evidences of inflammation. The individual components of the mass were concentrically placed laminated structures with a lumen. The authors called attention to the three outstanding theories advanced previous to this report, as to the pathogenesis of these hyaline deposits: (1) that they like the hyaline deposits in the lamina vitrea of the choroid are secreted from pigment epithelium which, in the case of drusen of the disk, has been misplaced on the papilla; (2) that they originate from exudate laid down in the nerve head by a previous inflammatory process; and (3) that they are derived from neuroglia. Goldstein and Givner favored the third theory since they found many hyaline deposits in the neuroglia itself. However, Duke-Elder stated: "All that can be said is that they seem to represent the deposition of a hyalin-like material because of some local metabolic disturbance of unknown and probably varied etiology."

In 1941, Samuels<sup>15</sup> reported the histopathologic characteristics of the drusen of the optic disk which he had encountered in the examination of 20 enucleated eyes, 7 of which had been removed because of secondary glaucoma. In one case, a drusen was located just posterior to the lamina cribrosa in the trunk of the optic nerve. In all other cases, the drusen were located anterior to the lamina cribrosa. Only 4 showed calcification. Samuels classified the drusen into intrapapillary, epipapillary and circum-papillary or transitional. The majority of the drusen were intrapapillary, in the middle and deeper layers of the papillæ, not near the vitreous surface. In one case, however, the drusen were on the surface of the disk embedded in a glial membrane. "Evidently these particular concretions were the product of a metaplastic process in new-formed neuroglia tissue." The glial membrane was thought to be a part of the reaction to a perforating ulcer of the cornea.

According to Samuels, drusen in the center of the papilla never show pigment. Drusen around the margin of the optic disk (circumpapillary or transitional drusen) may or may not show pigment. If they are non-pigmented, they may originate either from the papilla or from the retina. If they are pigmented, they arise from the pigment epithelium of the retina which has invaded the margin of the papilla. Samuels thinks apparently that atrophy of the optic nerve can be secondary to the presence of drusen. In his opinion drusen in the narrow unyielding sclerochoroidal canal would be more likely than those in the looser anterior tissues, to cause pressure atrophy of the nerve fibers and defects in the field of vision. He thought also that old calcified drusen might acquire a toxic and irritating effect on the nerve fibers. He regarded calcification as an indication of the greater age of the drusen.

With regard to the nature and pathogenesis of drusen, Samuels stated, "It is likely that every druse starts with a deposit of minute globules of hyaline which fuse and then increase in size by successive accessions. Separate drusen may coalesce to form large ones, which for this reason have uneven surfaces." He noted that glial cells may produce hyaline as shown by the finding of drusen in pure glial tissue on the surface of the retina and papilla. The mechanism of the formation of drusen was, he thought, an abnormal secretory activity of the glial cells of the papilla under the influence of irritation. He called attention to the fact that the papilla is particularly prone to produce drusen in pigmentary degeneration of the retina and in secondary glaucoma leading to gliosis of the retina

and he thought therefore that in many cases the drusen were the result of some local disease of long duration within the globe itself. He noted, however, that in some instances, drusen occurred in the otherwise normal eyes of young healthy individuals and he stated that "there is probably a constitutional basis for such early spontaneous growths."

It is noteworthy that, prior to the publication by Reese, no mention is made, except by Lauber,<sup>10</sup> in histopathologic descriptions of drusen of the optic disk of any definite associated cellular structures. Lauber noted that some large cells can be seen in close proximity to the smaller drusen. Apparently he did not attach any particular significance to these cells; but he noted some other cells which he thought were derived from the retinal pigment epithelium. Reese studied the histologic characteristics of the drusen found in the optic disks of 9 globes. Since these were found in a series of 893 enucleated eyes, Reese gives the probable incidence of drusen as 1%. This would seem to be higher than the probable expected incidence of at least ophthalmoscopically visible drusen. Five of the eyes studied by Reese were removed because of absolute glaucoma, one each because of buphthalmos, hydrophthalmos, malignant melanoma of the choroid, and traumatic detachment of the retina. Reese considered that the drusen were entirely independent of the other lesions in the eyes. They had been observed ophthalmoscopically in the optic disk of the fellow healthy eye in one case. According to Reese, the lesions were sharply demarcated, at times by a thin glial capsule. The main mass of the lesion was composed of conglomerate smaller masses with glial septa between them. Daughter lesions occurred around the main one. The bulk of the lesion was made up of calcium and an amorphous material, either hyaline or a closely related substance. Sometimes the lesion appeared to be concentrically lamellated around a central focus or to be arranged in crystal sheets. Cyst-like spaces appeared centrally in some lesions. Cellular elements were found immediately around or in the periphery of most but not all of the lesions. Cells with large oval nuclei tended to become shadow cells, then necrotic, and finally calcified within the lesion. Other cells had a large nucleus, distinct nucleolus, and a well-demarcated polygonal shaped protoplasmic border. Some of these cells contained a homogeneous refractile substance like that in the main lesion. Some of the smaller daughter areas resembled calcified cells. Reese thought that "the lesions represent a congenital excess of immature neuroglia which undergoes degeneration."

Reese noted the similarity between his findings and the histologic characteristics of the lesions found in the retina and optic disk in cases of tuberosus sclerosis. Messinger and Clarke<sup>12</sup> studied the tumor on the optic disk in a case which showed at necropsy typical lesions of tuberous sclerosis, multiple tumors of the brain, rhabdomyoma of the heart, lipofibromas of the kidneys, adenoma sebaceum of the Pringle type, and in the right eye a single, raised whitish tumor, 3 mm. in diameter, which covered the upper and inner two-thirds of the optic disk. The tumor involved all the layers of the retina and invaded a portion of the optic nerve. In the center of the tumor was a large irregular mass of ossification and around this were concretions containing calcium. At the periphery of the tumor was a thin layer of polymorphic tumor cells with indistinct boundaries and the suggestion of a syncytium. The cells had round or oval vesicular nuclei with a single nucleolus. The cells showed some vacuolation and some thick processes, some of which contained short fine glia fibrils.

According to Messinger and Clarke, only 4 histopathologic descriptions



of the retinal or disk lesions in tubercous sclerosis had been published previously. Schob<sup>17</sup> considered them to be gliomatous tumors. Fcriz<sup>4</sup> called them atypical neuroglia-like tissue. Kuchenmeister<sup>9</sup> found cells of varying type and shape and new-formed glial fibers. Van der Hoeve<sup>19</sup> suggested that the cells were descendants of the first anlage of the retina, neurocytes which had not differentiated into glia or ganglion cells or "glia neurocytes." He presumed that the tumors originated from embryonic cell rests and called them phakomata. In Messinger and Clarke's case, Ida Mann thought that the tumor developed or began to develop during the second stage of retinal differentiation (between the 6th week and the 3rd month of embryonal development) from glia cells of the inner neuroblastic layer with possibly a few undifferentiated ganglion and amacrine cells included. Messinger and Clarke were inclined to classify their tumor as a gliomatous hamartoma. Koch and Walsh<sup>8</sup> expressed the opinion that "the disease entity, tuberous sclerosis, appears to be the result of a developmental anomaly commencing early in fetal life and eventuating in widespread metaplasia which affects chiefly the ectodermal tissues but with subsequent prevalence of both mesodermal and entodermal derivatives."

Grinker<sup>7</sup> had suggested that the retinal tumors in tuberous sclerosis were probably astroblastic neoplasms of low growth potentialities. Tarlan stated that, in collaboration with McGrath, he had found, in a tumor of the optic nerve in a case of tuberous sclerosis, glial fibrils, absence of neurofibrillæ and typical perivascular feet. He considered that these findings proved that the tumor was an astroblastoma. He thought that the cells found by Reese bore a striking resemblance to astroblasts and he said, "While it is of course true that there is an urgent need for careful histologic study with differential staining, the evidence at hand certainly suggests that Dr. Reese's tumors are also astroblastic neoplasms of low growth potentialities and that they are at least related to, if not identical with, the manifestations of tuberous sclerosis." Reese himself thought that aside from the bone formation, his cases of drusen presented the same pathologic picture as that described by Messinger and Clarke in their tumor of the disk. Verhoeff<sup>21</sup> has noted ossification in drusen of the disk. Clinically, there is undoubtedly considerable similarity in appearance between hyaline bodies and the nodules making up the retinal and disk masses in tuberous sclerosis.

Reese concluded that "the findings in this study indicate that drusen of the optic nerve are a feature of the congenital developmental anomaly known as tuberous sclerosis. They may appear as a part of the fully developed protean disease but more frequently are seen as one of its many clinical variants or formes frustes." He stated that van der Hoeve<sup>19</sup> found a typical retinal tumor without any other manifestation of the disease in one member of a family in which siblings had had typical tuberous sclerosis. The classical clinical picture of tuberous sclerosis is mental deficiency, epilepsy, and adenoma sebaceum. Reese called attention to the well-recognized fact that disorders of the nervous system of one sort or the other are rather common in individuals who show drusen in the optic disk. In 18 of the 54 cases reported in the literature which Reese reviewed, there were mentioned such findings as convulsions, psychosis, disturbances of gait or speech, hydrocephalus, or papilledema. Renal dysfunction was noted in 7 cases, heart disease in 2, other congenital anomalies of the eye in 5, and retinitis pigmentosa in 7 cases.

Though instability of the nervous system is often striking in individuals

presenting drusen of the optic disk and in members of their immediate family, it must be remembered that actual organic cerebral disease of the type seen in tuberous sclerosis has not as yet been definitely demonstrated in association with typical simple drusen of the disks. Small areas of cerebral calcification such as are seen in roentgenograms of the head in cases of tuberous sclerosis have not been demonstrated in association with drusen. Among the 3 clinically observed cases reported by Reese, examination of the nervous system was not carried out in 1 and yielded negative results in 2. Roentgenograms of the head were negative in 2 cases and a ventriculogram was negative in 1. Pneumoencephalograms were negative in 2 cases reported by Schlezinger, Waldman and Alpers.<sup>16</sup> In one of these cases, an electroencephalogram showed showers of sharp and slow wave formations in the left frontal and parietal areas which were of questionable significance.

Electroencephalograms have been done at the Mayo Clinic on 6 patients who had drusen in the optic disks. The results were interesting though probably not clinically significant. Two were reported as essentially normal. In one of these patients, an electroencephalogram done previously elsewhere was said to show some dysrhythmia. At the time of our examination there was slight delta activity in the right temporal area. In a third patient who presented a post-head injury syndrome, the electroencephalogram gave a low potential record but was otherwise negative. A pneumoencephalogram was normal. In the fourth case, the electroencephalogram showed some dysrhythmia; in the fifth, dysrhythmia and bilateral occipital delta activity Grade 1 to 2, and in the sixth, generalized dysrhythmia. The fifth patient, in whom the drusen were unilateral, had no presenting complaints except myopia. The electroencephalographic findings, the appearance of the optic disks, and the field defect, an inferior arcuate scotoma, had remained unchanged at the end of 9 months. In all these cases except the sixth, roentgenograms of the head were normal. In the sixth case, the sella was enlarged and the dorsum eroded. In 3 of the cases, examination of the central nervous system was objectively normal. One of the patients presented an Adie's syndrome, one had syphilis of the central nervous system with positive serology in the spinal fluid, and the sixth had, along with emotional instability, signs of an organic brain disorder of indeterminate nature mainly in the cerebellum.

So far as I have been able to determine there have been no reports in cases of drusen in the disks of histologic changes in the brain similar to those found in tuberous sclerosis. In Lauber's case, the brain was said to be normal; the optic nerve was atrophic. In the case reported by de Schweinitz,<sup>18</sup> the patient had had mental symptoms and the brain was said to show ependymitis with ventricular dilatation. The optic nerves were atrophic. However, there were no histopathologic changes demonstrable in the brain substance or in the other cranial nerves. In de Schweinitz's opinion, the negative findings in the brain and in the other cranial nerves indicated that the formation of drusen in the optic disk is a purely local process, the nature of which is unknown. He did not think that the drusen were produced by the process which caused the atrophy of the optic nerves.

As noted by Reese,<sup>18</sup> tuberous sclerosis is a heredofamilial disease. Duke-Elder states that it has been observed in identical twins and that it has been reported in three generations of one family. Drusen of the optic disk also have been observed to have familial and hereditary incidence. Lauber<sup>10</sup> observed drusen of the disk in a mother and 2 daughters. Ancke<sup>1</sup>

found them in several members of two families in association with retinitis pigmentosa. On the basis of his observations in two families, Braun<sup>2</sup> considered the tendency to drusen formation to be an hereditary dominant. He found drusen in a mother and one daughter and one son. In the other family group reported, the findings were somewhat questionable. Leimgruber<sup>11</sup> reported his observations on drusen of the optic disks among the members of five families. In Family 1, drusen were found in 6 out of 9 sisters and brothers and also in 2 of their children. In Family 2, drusen were seen in 2 sisters; in Family 3, in 2 brothers, and in Family 4, in identical twins. In Family 5, a woman and her son were affected.

Although it cannot be considered to be definitely proved at present that drusen of the optic disk are really slow growing astroblastomas of hereditary and familial occurrence and that they represent a variant of tuberous sclerosis, the evidence presented is at least suggestive and intriguing and warrants further study and investigation. For as Reese points out, "If this conclusion is correct, drusen of the optic nerve assume new significance as a familial developmental defect which is frequently associated in the patient, in his progenitors, in siblings, or in offspring with serious involvement of the central nervous system, and rarely, with renal and cardiac lesions."

#### REFERENCES

- (1.) Ancke, R.: *Centralbl. f. prakt. Augenh.*, 5, 167, 1885. (2.) Braun, W.: *Klin. Monatsbl. f. Augenh.*, 94, 734, 1935. (3.) Duke-Elder, Sir W. S.: *Text-Book of Ophthalmology*, 3, 2857, 3062, 1942. (4.) Feriz, H.: *Virchows Arch. f. path. Anat.*, 278, 690, 1930. (5.) Fuchs, A.: *Atlas der Histopathologie des Auges*, Vienna, 1927. (6.) Goldstein, I., and Givner, I.: *Arch. Ophth.*, 10, 76, 1933. (7.) Grinker, R. R.: *Cytology and Cellular Pathology of the Nervous System* (Penfield, W.), New York, Hoeber, p. 1058, 1932. (8.) Koch, F. L. P., and Walsh, M. N.: *Arch. Ophth.*, 21, 465, 1939. (9.) Kuchenmeister, E.: *Dermat. Wehnschr.*, 99, 1333, 1934. (10.) Lauber, H.: *Arch. f. Ophth.*, 105, 567, 1921. (11.) Leimgruber, M.: *Arch. f. Ophth.*, 136, 364, 1936-37. (12.) Messinger, H. C., and Clarke, B. E.: *Arch. Ophth.*, 18, 1, 1937. (13.) Reese, A. B.: *Arch. Ophth.*, 24, 187, 1940. (14.) Rucker, C. W.: *Arch. f. Ophth.*, 32, 56, 1944. (15.) Samuels, B.: *Arch. Ophth.*, 25, 412, 1941. (16.) Schlezinger, N. S., Waldman, J., and Alpers, B. J.: *Arch. Ophth.*, 31, 509, 1944. (17.) Schob, F.: *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 95, 731, 1925. (18.) de Schweinitz, G. E.: *Trans. Am. Ophth. Soc.*, 6, 349, 1891. (19.) van der Hoeve, J.: *Arch. f. Ophth.*, 105, 880, 1921; 111, 1, 1923. (20.) Tarlan, M. N.: Discussion of Reese, A. B. (21.) Verhoeff, F. H.: Discussion of Samuels, B.<sup>15</sup>

# BOOK REVIEWS AND NOTICES

---

**CLINICAL ROENTGENOLOGY OF THE DIGESTIVE TRACT.** By MAURICE FELDMAN, M.D., Assistant Professor of Gastroenterology, Univ. of Maryland; Assistant in Gastroenterology, Mercy Hospital; Consulting Roentgenologist, Sinai Hospital. Second Ed. Pp. 769; 550 figs. Baltimore: Williams & Wilkins, 1945. Price, \$7.00.

THE 2nd edition of this book is exactly what its title indicates. The author has provided in a unique way not only pertinent roentgenologic diagnostic criteria but has included the clinical considerations as well. Such a book is of extreme value not only to the clinician doing his own Roentgen studies of the gastro-intestinal tract but to the medical radiologist as well. In almost every lesion the author considers the incidence, the etiology, symptoms, pathologic manifestation of the primary lesion and any complication thereof. Such a book provides for the radiologist a quick reference book and the book can be resorted to as a reference book in the true sense of the word. The author has quoted from many publications.

The book is profusely illustrated and there are a number of pen and pencil drawings. Likewise the author has included in addition to the usual and more frequent gastro-intestinal lesions, a number of the various anomalies and rare conditions.

The publisher is to be congratulated on the type of paper that has been used and the excellence of the printing and illustrations. E. P.

---

**PENICILLIN THERAPY** Including Thyrothricin and Other Antibiotic Therapy. By JOHN A. KOLMER, M.S., M.D., DR.P.H., Sc.D., LL.D., L.H.D., F.A.C.P., Professor of Medicine in the School of Medicine and the School of Dentistry, Temple Univ.; Director of the Research Institute of Cutaneous Medicine; Formerly Professor of Pathology and Bacteriology, Graduate School of Medicine, Univ. of Pennsylvania. Pp. 302; 22 figs. New York: London: Appleton-Century, 1945.

Now that penicillin has become available commercially as a therapeutic agent, there is a need for a clear statement of its pharmacodynamics, the indications and contraindications for its use, and the methods available for its administration. Dr. Kolmer's book fulfils this need as well as our present knowledge permits. As he points out, it is amazing and pleasant to realize that penicillin has progressed in 4 years from a bacteriologic curiosity to the most powerful weapon of the modern therapeutic armamentarium. In the monograph, his approach has been a review of all of the most important articles in the literature on the subject of penicillin. Coverage of the literature has been complete but not redundant, ranging from a consideration of the optimal media on which the mold has been grown to the manifold clinical uses of penicillin. Dr. Kolmer's review is completely up-to-date, as is shown by his inclusion of the latest literature on the oral administration of penicillin and on penicillin F., G., and X. with references as late as 1945.

This work is of especial interest to laboratory men, since all of present acceptable methods of detection and assay have been well described, and he has discussed those physical and chemical properties that necessitate special handling of the drug.

Most clinicians are well aware of the more important indications for the use of penicillin, but the modes of administration other than intramuscular are often seriously neglected. Examples of this are the failure to use intrapleural penicillin in empyema and intracisternal penicillin in the severe meningitides.

These techniques along with proper dosage schedules are thoroughly covered. As indicated by the title, the book includes an adequate account of the other important antibiotics such as streptomycin and thyrothricin now under experimental and therapeutic consideration.

Dr. Kolmer's work provides an excellent summary of a field in which the accumulated literature has become too voluminous for most of us to cover. This volume should be of great importance to all medical men whether they be students, *general practitioners, surgeons, internists or laboratory men.*

R. M.

**MASS RADIOGRAPHY OF THE CHEST.** By HERMAN E. HILLEBOE, M.D., Medical Director, Chief, Tuberculosis Control Division, U. S. P. H. S.; Professorial Lecturer on Tuberculosis Control, George Washington Univ. School of Medicine, Washington, D. C.; and RUSSELL H. MORGAN, M.D., Surgeon (R), Medical Officer-in-Charge, Radiology Section, Tuberculosis Control Division, U. S. P. H. S. Pp. 288; 93 figs. Chicago: Year Book Publishers, 1945. Price, \$3.50.

THIS little manual of 13 chapters is one of the real contributions to medicine. Although our knowledge in tuberculosis has increased in many ways, no real contribution has been made in the field of prevention. There is no specific cure or any effective immunizing agent against the disease. The development of mass radiography of the chest has provided a method whereby it has become possible to discover the sources of the infection and thereby render it possible for each community to make a direct attack upon the tuberculosis problem.

There are no two men in the world who have contributed more to this subject and to the development of the methods of mass radiography than have Drs. Hilleboe and Morgan. Through their intelligent efforts, the world is being provided with a program which should largely eradicate tuberculosis.

For anyone interested in this subject, and it should be of interest to all medical men as well as all public health physicians, Drs. Hilleboe and Morgan have, in a comprehensive way, written an effective manual on the objectives of tuberculosis control; the community planning of such a program; considerations about the equipment to be used; the Roentgen technique of a mass radiography; considerations concerned with the Roentgen diagnosis of lesions in the chest and other important items concerned with such an undertaking.

Some of these observations have been made by others as well as by the authors; but for the most part, this manual is the first comprehensive treatise on this subject and one finds it difficult not to be too enthusiastic.

The publisher is to be congratulated on the general make-up of the manual, the illustrations, the paper and the printing. This is a book that should be of interest to every physician.

E. P.

**THE NEW-BORN INFANT.** A Manual of Obstetrical Pediatrics. By EMERSON L. STONE, M.D., Associate Clinical Professor of Obstetrics and Gynecology, School of Medicine, Yale Univ.; Attending Obstetrician and Gynecologist to The New Haven Hosp. Third Ed. Pp. 314. Philadelphia: Lea & Febiger, 1945. Price, \$3.25.

THIS handy monograph discusses clearly and comprehensively the problems of nursing care, feeding and feeding disorders, birth injuries, infections and disorders of specific organ systems as they present themselves in the neonatal period. The contents are well organized and up-to-date and reflect the modern point of view. One may question the propriety of advocating toilet training as early as 2 weeks of age, or of giving the vitamin C content of orange juice in terms of "units" rather than milligrams. This edition appears to have gone to press prior to the discovery of the relationship of maternal German measles to infantile malformations and of prematurity to eye lesions; but the Rh factor and the relationship between diabetes in the mother and cardiac enlargement receive specific mention.

Every obstetrician, pediatrician and general practitioner who assumes responsibility for the care of newborn infants, whether in nurseries or private homes, should have at his finger-tips the information contained in this handy volume. I. W.

**MARIHUANA PROBLEMS**—in the City of New York. Sociological, Medical, Psychological and Pharmacological Studies. By the Mayor's Committee on Marihuana. Pp. 220. Lancaster: Jaques Cattell, 1944. Price, \$2.50.

THIS monograph is the result of a study carried out by the Mayor's Committee of the City of New York in response to rumors that marihuana smoking was common among large segments of the city population and was even indulged in by school children. The study reveals that the assertions leading to the study were exaggerated; but the medical profession and the general population have profited by a serious investigation of the sociologic, medical, psychologic and pharmacologic features of marihuana smoking. Among the significant conclusions of the study are that marihuana smoking does not lead to addiction in the medical sense of the word; that it does not lead to heroin, morphine or cocaine addiction; that it is not the determining factor in the commission of crimes; that it is not widespread among school children; and that juvenile delinquency is not associated with the practice of smoking marihuana. Body steadiness and hand steadiness are most seriously affected by the drug. Psychologic studies reveal that marihuana induces feelings of relaxation, disinhibition, and self-confidence. The studies of the pharmacologic action of the drug are extensive and well done.

The investigation has been thorough and inclusive and constitutes a serious contribution to the effects of marihuana on the body and emotions. It can be recommended highly to social workers, physicians, and lay readers.

**INFANTS AND CHILDREN. Their Feeding and Growth.** By FREDERIC H. BARTLETT, M.D., Attending Pediatrician, Babies' Hosp., New York City. Sixteenth Ed. Pp. 428. New York: Farrar & Rinehart, 1945. Price, \$2.00.

ANY book for parents which passes through 16 printings in 13 years must have a popular appeal and meet a mass need. This well-known one by Bartlett is full of instructions on the common every-day problems of infant and child rearing. Its distinctive quality is its lively conversational style. The information is broad in scope and sound in character, yet not so meticulous and detailed that the layman will be tempted to use it as a substitute for skilled medical supervision. I. W.

**THE EXAMINATION OF REFLEXES.** By ROBERT WARTENBERG, M.D. Foreword by FOSTER KENNEDY, M.D. Pp. 222. Chicago: Year Book Publ., 1945. Price, \$2.50.

A SYSTEMATIC synthesis of some of the numerous deep muscle reflexes is presented. Twenty-five muscle reflexes are critically described and discussed, from the orbicularis oculi reflex to the distant toe flexor reflex. The author's basic principles are as follows:

The most important reflexive stimulus for the muscle consists of a sudden, brief concussion and stretching of the muscle tissue. The contraction of a muscle on being stretched may exist in latent form and become apparent only when there is a functional or an organic increase in muscle tonus. Since concussion of the muscle and its stretching constitutes the true cause of the deep muscle reflex, the point from which the response may be achieved is not essential. Every muscle crosses one or more joints and is comparable therefore to a tautly-drawn bowstring. Sudden stretching of such a string may be achieved by a force acting either on the plane or on the convex side of the bow mechanism. Therefore, the possibility of elicitation of a deep muscle reflex by striking the bone offers much to the comprehension of many misun-

derstood and misnamed reflex phenomena. The transmission of concussion through the bone makes it understandable that under favorable conditions a single tap with the reflex hammer may affect several functionally different muscles and thus evoke multiple, but completely independent, unrelated reflexes. A reflex should be named according to the acting muscle, not according to the point of stimulation. For a given reflex the muscle is always the same, but the place of stimulation may vary considerably. The term tendon reflexes should not be used because stimulation of the tendon cannot evoke any reflex action unless the muscle tissue is influenced through the tendon. There is no such thing as a tendon stretch reflex. The same applies to so-called bone, periosteal, osteoperiosteal, osteo-tendon, joint, fascial reflexes. Reflexes which do not fit into the regular reflex pattern are often called paradoxical, inverted or antagonistic. There is nothing paradoxical about them; they are simply occasional forms of well-known deep reflexes appearing under certain conditions and depending on particular techniques applied in their elicitation.

In the foregoing manner, Dr. Wartenberg indicates the premises on which his physiologic approach to the muscle reflex problem is made. Carefully worded description of method and technique is adhered to throughout the monograph. Every student of the subject should find the book interesting, stimulating and thought-provoking.

A. O.

**DISEASES OF THE NERVOUS SYSTEM IN INFANCY, CHILDHOOD AND ADOLESCENCE.** By FRANK R. FORD, M.D., Associate Professor of Neurology, Johns Hopkins Univ. Second Ed. Pp. 1143. Springfield, Ill.: Thomas, 1944. Price, \$12.50.

In its new and expanded form, Ford's text-book maintains its preëminent position. Every disease of childhood which may have nervous system complications is specifically mentioned, and of course those conditions which are primarily neurologic in character receive full discussion. Child psychiatry is wisely not included. The classification of subjects is by etiology rather than by organ systems, with 2 excellent-introductory chapters on examination and clinical anatomy and physiology. Every doctor—whether pediatrician, neurologist, internist or general practitioner—who has to cope with child patients ill with nervous system diseases, would be wise to own and use this book as a desktop reference.

I. W.

**FOSTER HOME CARE OF MENTAL PATIENTS.** By HESTER B. CRUTCHER, Director of Social Work, State of New York, Department of Mental Hygiene. Foreword by ARTHUR H. RUGGLES, M.D. Pp. 199. New York: Commonwealth Fund, 1944. Price, \$2.00.

THIS unusually valuable treatise tells how the mentally ill may receive excellent extramural care. Two methods are employed: the colony plan and the district plan wherein the patients are scattered. The sites of choice for foster homes are small towns or suitable country locations. The various chapters discuss Family Care: Its Meaning and Values; Administration and Results of Family Care; Family Care as a Therapeutic Procedure; Selection of Patients; Selection of Homes; Supervision of Patients; Two Methods of Organizing Family Care; Some Case Histories; Suggested Forms and Procedures.

There is also an Appendix on Family Care Programs in the United States. Patients may be selected from the præcox group; senile subjects who only require individual attention and kindness; those whose dissatisfactions with hospital treatment decrease with family care; those unable to adjust outside the hospital; those with paranoid trends impossible to adjust among former associates; those having emotional needs met and security somewhat restored by family care. Among those who should not be permitted such freedom are subjects who become excited, noisy and violent, suicidal, homicidal, those

with erotic tendencies or who attempt to escape, and alcoholic and narcotic addicts. To the colonists come the advantages of home comforts, normal associations, greater freedom and suitable work. The foster families obtain fuller economic security. Fewer buildings would lessen the taxpayers' burden. Still another advantage—promotion of a better understanding among the public toward mental patients, of whom it is sometimes too fearful.

N. Y.

---

IMMUNO-CATALYSIS. By M. G. SEVAG, PH.D., Assistant Professor of Biochemistry in Bacteriology, Department of Bacteriology, School of Medicine, Univ. of Pennsylvania. With a Preface by STUART MUDD, M.A., M.D., Professor of Bacteriology, Univ. of Pennsylvania. Pp. 272. Springfield, Ill.: Thomas, 1945. Price, \$4.50.

THE author has written a very stimulating treatise which will undoubtedly arouse mixed emotions in its readers. Starting with the concept that specific antibody formation is essentially a catalytic or enzyme process, the author has collected and integrated an imposing mass of information. Thus antigens are treated as specific enzymes, antibody precursors as enzyme substrates, and antibodies as specific enzyme inhibitors. Although this idea has been expressed before, here for the first time is an attempt to demonstrate conclusively that the facts fit the criteria of ideal catalysis. As a further extension of this concept the author states: "If . . . we define an enzyme as any protein capable of performing a specialized physiological function in accordance with the well known criteria of ideal catalysis, a comprehensive theory of biocatalysis is provided which links antigens, enzymes, vitamins and hormones and possibly other still unknown substances of similar role." With this concept many will disagree, as the author freely admits. The term enzyme has served in the past as a useful description of proteins which are capable of initiating or stimulating specific catalytic processes in isolated or *in vitro* systems as well as in the complex living organism. To include in this category all proteins exerting a specific biologic effect in the living organism is decidedly a new concept. The Reviewer has no doubt that a splinter driven into the hand will elicit a specific response and might therefore be reasonably called a biocatalyst or even an enzyme. Also, there is surely no need to restrict this all inclusive generalization to proteins. However, this extension of Sevag's ideas to what may appear to be an absurdity does not alter the fact that perhaps the time has come to revise our concepts if only to bring about and stimulate new thought.

The work is divided into 5 main parts: I. Antigens as Biocatalysts; II. Antibody as a Specific Enzyme Inhibitor; III. Anti-enzyme Immunity; IV. Immunity Against Bacterial Enzymes; V. The Problem of Antibody Formation Against Respiratory Enzymes. There is considerable discussion of such interesting topics as antibodies against hydrolytic enzymes, snake venoms, toxins, hemolysins, fibrolysin, hyaluronidase and the relation of these phenomena to the problems of infectious disease.

The book is well written; the printing and binding are excellent. There are a few errors in the organic structures and some loose usage of the terms tautomerism, stereoisomerism, and geometric isomerism. The diagram illustrating the mutarotation of glucose (p. 25) is confusing. These are, however, minor errors which will undoubtedly be corrected in subsequent editions.

This book will be of interest to bacteriologists, immunologists and biochemists. Biochemists, in particular, will find here a stimulating and fertile field for research. It is only fair to state that the underlying concept, based as it is upon chemical principles, is nevertheless a convenient theory and not an accepted fact. Used with reservations, it can serve as a stimulus for new ideas; accepted blindly and without critical judgment, it may lead the unwary into a morass of confusion. It is to the author's credit that he has courageously set forth a challenge and defended it skilfully and honestly.

S. G.



**MICROBIAL ANTAGONISMS AND ANTIBIOTIC SUBSTANCES.** By SELMAN A. WAKSMAN, Professor of Microbiology, Rutgers Univ.; Microbiologist, New Jersey Agricultural Experiment Station. Pp. 350 + IX. New York: Commonwealth Fund, 1945. Price, \$3.75.

THIS book, the first on the subject of antibiotics, appears at an opportune time to be helpful to those interested in the subject. The material is presented from the biologic viewpoint in a scholarly manner. It compiles and organizes the information on antibiotics. The book describes methods for searching for organisms which show bacterial antagonism, methods for producing antibacterial substances, testing their action against microorganisms and determining possible therapeutic uses. The properties of many antibiotic substances are discussed. The book contains a classification of many antibiotics according to the microorganisms producing them, a glossary of terms used in describing antibiotics, an index of microorganisms cited in the text, a very complete general index and a valuable bibliography of over 1000 citations of the literature.

H. M.

**MODERN PSYCHIATRY.** By WILLIAM S. SADLER, M.D., F.A.P.A., Chicago, Consulting Psychiatrist to Columbus Hosp.; Consultant in Psychiatry, The K. W. Kellogg Foundation; Fellow of the American Psychiatric Association; Member of the American Psychopathologic Association. Pp. 869. St. Louis: Mosby, 1945. Price, \$10.00.

COINING the word *personology*, and asserting it should be in the dictionary, the writer proceeds to explain the difficulties human beings have in adjusting themselves to life. The book is for general practitioners, specialists and psychiatrists, and considers the problems of personality maladjustment, the psychoneuroses and psychoses. Its purpose is "a ready and compact reference book for diagnosis and immediate treatment." The Introduction is given over entirely to Psychosomatic Medicine which includes about 25% of the patients who visit physicians. Its 61 chapters are discussed in 4 parts: Personality Problems, The Psychoneuroses, The Psychoses, and General Psychotherapeutics which is given considerable space. The manic-depressive psychoses are accorded more space than any other subject, with the writer saying they result from inherent defects in the nervous system and the metabolic mechanism. A subdivision is manias, depressions and mixed states, each of which undergoes a further subdivision. Among the important hypnotics are sodium amytal and paraldehyde, the former being preferable. It is believed a manic attack can be shortened by deep continuous narcosis with sodium amytal. The schizophrenic reaction type presents the real mystery in psychiatry, with 40,000 new patients occurring annually in the United States, and which constitute about 50% of institution population. When early treatment is instituted, the prognosis is more favorable than formerly. Shock therapy and massive doses of sodium amytal are proving of distinct use. Speaking of the psychoneuroses, the writer estimates that half the patients seen in general practice show more or less neurotic disturbances. "*Never forget!* The average neurotic patient does not really desire to be cured of his neuroticism—he merely wants to secure relief from his numerous distressing and disabling symptoms." After telling of some 15 other theories as to the causes of the neuroses, the writer gives what he terms the Comprehensive Working Theory, embracing at least 3 constant and ever-interlacing factors: (1) Emotional conflict of some sort. (2) Hyperirritability of the vegetative nervous system. (3) Functional and associated endocrine disturbances of varying and ever-changing nature. As to the inferiority complex, stress is laid on the fact that often in early life parents unwittingly cause the child to feel his inferiority; also, a state of chronic discouragement may supervene if too much is expected of the child. The value of narco-analysis of Horsley and others is given scant consideration. In an Appendix the schools of psychiatry are discussed and a Glossary of 34 pages is included. The text covers a vast expanse in psychiatry and is replete with valuable information and stimulating suggestions.

N. Y.

THE RETICULO-ENDOTHELIAL SYSTEM IN SULFONAMIDE ACTIVITY. By FRANK THOMAS MAHER, PH.D., Assistant Professor of Pharmacognosy and Pharmacology. Contribution from the Dept. of Pharmacology, Materia Medica, and Therapeutics in the College of Medicine. Pp. 232; numerous figs. and tables. Urbana, Ill.: The Univ. of Illinois Press, 1944. Price, \$2.50.

THIS comprises the first 2 numbers of Volume V of University of Illinois Medical and Dental Monographs. It consists of a compilation of the literature bearing on the sulfonamides up to the end of 1941 and a report of the author's own experiments on the influence of blockade of the reticulo-endothelial system (by thorotrast) on the life-saving effects of sulfanilamide and sulfathiazole in rabbits inoculated with streptococci and staphylococci. The results support the general belief that body defense mechanisms play a determining rôle in sulfonamide therapy, but they contribute nothing to an understanding of the factors involved either in the drug action or in the functions of the reticulo-endothelial system. The presentation is extremely detailed and unnecessarily repetitious. The discussions take no account of the work done in this field since 1941 and therefore have more historical than current importance.

C. S.

MEDICAL CLINICS OF NORTH AMERICA. Chicago Number, January 1945. Symposium on Neuropsychiatric Diseases. Pp. 271. Phila.: Saunders. Price, \$16.00, year.

THE selection of topics for this symposium was timely. "Discs" are frequently seen in industry and combat operations. Peripheral nerve injury is being inflicted too frequently on every battle front. Likewise the Guillian-Barré syndrome is being seen in almost epidemic proportions. The understanding of the psychiatric approach to criminology needs more stress.

The articles are presented clearly, with the possible exception of the *Modern Concept of Schizophrenia*. Only a few omissions can be noted, such as the lack of stress on facial diplegia as part of the Guillian-Barré syndrome and the importance of overlap in peripheral nerve distribution. The electrical reaction of injured nerves was not too clearly put. Especially well presented in the excellent style of the author were the facial pain article by Dr. Walker, subdural hematoma by Dr. Oldberg, insomnia by Dr. Solomon and cordotomy by Dr. Verbrugghen. The articles on myasthenia and periarteritis reviewed the important points in the literature. Electro-shock to out-patients is interesting and well analyzed. This number of the Clinics is a valuable contribution.

J. T.

THE HUMAN MIND. By KARL A. MENNINGER, M.D. Third Ed. Pp. 517; 15 figures. New York: Alfred A. Knopf, 1945. Price, \$5.00.

OF the preceding edition, more than 200,000 copies were sold in the United States. The present issue has been "corrected, enlarged and rewritten." The additional matter includes "achievement tests," "alcoholic anonymous," "The American Psychiatric Association," and "electroencephalography." Since an "organic personality type" was mentioned in the 1st edition, the writer now takes pride in his anticipation of psychosomatic medicine though the term is unfortunate, since it implies a duality of mind and body. But little retreat is shown from the previous stand on psychoanalysis as the most important form of mental hygiene. The chapters are: Principles, Personalities, Symptoms, Motives, Treatments and Applications. Though not strictly systematic, a practical and descriptive classification of personalities is given as: crippled, stupid, lonely, queer, and perverse personalities. Under Treatments, while brief reference to "narcosynthesis" is made, the important narcosis of Horsley and others, receives no definite consideration. In Symptoms, the dismantled parts of the machine are dealt with analytically. Motives is a dynamic section wherein the source and distribution of the power driving the machine is considered. Treatments, gives the technique of repair making. Applications deals fundamentally with extensions of psychiatric theory.

N. Y.

**FUNDAMENTALS OF PHARMACOLOGY.** By CLINTON H. THIENES, M.D., Ph.D., Professor of Pharmacology, Univ. of Southern California School of Medicine. Pp. 444; 36 figs. New York and London: Hoeber, 1945. Price, \$5.75.

THIS concise volume is the textbook on pharmacology in the "Medical Students' Series" designed to "offer the medical student a volume which presents the basis of the subject in such form and degree of detail as he can absorb in the time allotted." It is no easy task to make from a vast wealth of knowledge a selection of fundamental material upon which everyone will unqualifiedly agree. On the whole this book is well and concisely written, logically organized and up to date (including discussions of penicillin, sulfadiazine and thiouracil). It adequately satisfies the need for which it was written.

It must be conceded, however, that this volume or any textbook so conceived accomplishes its objective of brevity only at the sacrifice of information which many in the field would consider important. In the past decade there has been a notable emphasis on the effects of drugs in man, made possible by the development of new methods of clinical investigation; yet this phase of pharmacology appears somewhat neglected. Since data are available on cardiac output and left ventricular work following the administration of therapeutic doses of some important circulatory drugs in man, it would seem well to mention them. The section on renal physiology and diuretics neglects results obtained by techniques now several years old for studying human renal physiology and pharmacology. On the other hand, there is the inclusion and even the emphasis of certain information which could well be left to a more encyclopedic work. Pedagogic technique seems hardly to justify devoting as much space to strychnine, the therapeutic usefulness of which is today thought to be practically *nil*, as to the belladonna group. The consideration of aconite and veratrum and their dosages seems unwarranted. The discussion of toxicology is restricted to substances used therapeutically, so that an important disease like lead poisoning receives no consideration.

In most other respects, however, the book is a worthwhile text and the student who desires a clear, concise and readily assimilable presentation of the subject will find it very useful.

S. K.

**TEXTBOOK OF NEUROPATHOLOGY.** By ARTHUR WEIL, M.D., Associate Professor of Neuropathology, Northwestern Univ. Medical School. Second Ed. Pp. 370; 289 ills. New York: Grune & Stratton, 1945. Price, \$5.50.

THERE is not great change in the 2nd edition, nor can one expect neuropathology to change greatly in a decade between the 2 editions of this work. It is a clear and concise outline of the macroscopic and microscopic pathology of the nervous system. An interesting feature is the attention given by the author to physical and chemical data pertaining to the brain and its post-mortem changes. The new edition takes cognizance of the great strides made in neuropsychiatry through a better understanding of vitamin deficiencies, chemotherapy and shock treatment. Dr. Weil calls attention to the newer conception of the virus infections as well as adding more data on protozoal infections of the nervous system. The 1st edition served as an authoritative text for students and there is every reason to believe that the 2nd edition will be just as popular. The book has been enlarged and 27 plates added.

A. O.

**THE BASIS OF CLINICAL NEUROLOGY.** The Anatomy and Physiology of the Nervous System in Their Application to Clinical Neurology. By SAMUEL BROCK, M.D., Professor of Neurology, College of Medicine, New York Univ. Second Ed. Pp. 393; 72 figs. Baltimore: Williams & Wilkins, 1945. Price, \$5.50.

THIS 2nd edition of Dr. Brock's deservedly vaunted book has been rather extensively revised because of the great advances in neurophysiology produced

by laboratory investigators and neurosurgeons. He has, as in the 1st edition, maintained the emphasis on the clinical application of the newer knowledge gained both in neurophysiology and neuroanatomy. In their respective chapters 3 collaborators have added electrodiagnostic methods, physiology of urination and cystometry and electroencephalography, respectively. The amplified text reflects the author's extensive experience as a clinician and his keen appreciation of clinical phenomena. This combined with the morphology, physiology and pathology of the nervous system makes the work an invaluable guide to the sound and practical interpretation of nervous diseases. From this standpoint it is an unusual book on clinical neurology worthy of the close attention of student, clinician and teacher alike. A. O.

---

COMMON AILMENTS OF MAN. Edited by MORRIS FISHBEIN, M.D., Editor, *Hygeia*, The Health Magazine. Pp. 177. New York: Garden City Publ. Co., 9th Copyright, 1945. Price, \$1.00.

THIS is the 9th of a series of reprints from *Hygeia*, the American Medical Association's health magazine for the public. The 16 articles cover our commonest ailments and symptoms—a good half having been written by nationally recognized authorities. Carefully warning against the error of improper self treatment, they should be helpful in informing the layman to understand his physical ailments and to know when to seek expert help. E. K.

---

MEN UNDER STRESS. By ROY R. GRINKER, LT. COL., M.C., and JOHN P. SPIEGEL, MAJOR, M.C. Pp. 484; 2 tables. Phila.: Blakiston, 1945. Price, \$5.00.

THE first Army Air Forces convalescent hospital in this country, caring exclusively for "Operational Fatigue" sufferers, was established by these authors. Though several thousand cases were seen by them; lack of space has prevented the recording of but 65; a number of their subjects were given sodium pentothal to facilitate abreaction, then following with appropriate psychotherapy. The text is discussed in the following Parts: The Man; The Environment of Combat; The Reactions to Combat—Morale; The Reactions After Combat; Civilian Applications. Reactions After Combat is most important and is treated as: The Return Home; The Syndrome of "Operational Fatigue" (war neuroses) in Returnees; Passive-Dependent States; Psychosomatic States; Guilt and Depression; Aggressive and Hostile Reactions; Psychotic-like States; Psychodynamics; Psychotherapy; Narcosynthesis; Adjunctive Treatment; and Results.

In regard to narcosynthesis: when time permits, psychiatric interviews while the patient is fully conscious, yields the necessary material and emotional release; but during combat, a shortcut is necessary, and in approximately half of their subjects, such a procedure was required. The drug of choice is sodium pentothal, which acts more promptly than other drugs; a slow intravenous injection is made until the proper stage of narcosis is obtained. Alcoholics do not respond satisfactorily, so that patients must not drink for hours before the injection. Skill is required to obtain the best results. The information gained by shortening the time should be of value in civilian psychiatry. Narcosis, or continuous sleep treatment, was not promising; the drug of choice is sodium amytal; the duration of sleep varied from 27 to 110 hours. Of 20 patients so treated, only 3 showed improvement, and the rest were unimproved or made worse.

As the number of subjects needing treatment is large, and as recreational and occupational therapy are not sufficient for the needs of many, *group psychotherapy* is being widely employed; for this, some special training is required. Two methods are employed: in the repressive-inspirational method, the effort is to "urge, persuade and force the patient to control himself, to suppress asocial or worrisome thoughts. Interest or inspiration in life work, the community, religion, art, music, etc., is encouraged." The analytic method

"urges the loosening of repression and feeling of urges bound up in repression. It strives for the conscious recognition and analysis of unconscious and asocial wishes and trends." The 2 methods may be combined. This book is timely and important. N. Y.

**CLINICAL ATLAS OF BLOOD DISEASES.** By A. PINEY, M.D., M.R.C.P., Physician, St. Mary's Hospital for Women and Children; and STANLEY WYARD, M.D., F.R.C.P., Physician, The Royal Cancer Hospital, London, and Princess Beatrice Hospital. Sixth Ed. With 48 illustrations, 45 in color.

This practical guide, by the use of "telegraphic" style consistently followed, and oriented by different kinds of type, gives valuable help to the busy practitioner. The authoritative authorship and the many colored plates (somewhat too diagrammatic) with a synopsis of the symptoms, diagnosis, patho-diagnosis, etiology, pathology, and treatment opposite each plate, still further add to its usefulness. E. K.

**THE MALE HORMONE.** By PAUL DE KRUIF. New York: Harcourt, Brace & Co., 1945. Price, \$2.50.

If this book confined itself to telling, as the cover states, "without blushes or polite evasions the story of the discovery of the male hormone," it would not be subject to blame, nor would it be a "best seller." But when, again to quote from the cover, "It boosts muscle power. It banishes mental fatigue. It eases heart pain. It even restores the sanity of men in midlife who suffer male hormone hunger; seems to renew the tissues of ageing men. It brings a gleam of hope for the extension of the working, vigorous lives of millions of Americans," then it exceeds the bounds of propriety and of legitimate popular medicine writing. Testosterone is known to be a potent drug and its therapeutic values are being studied by many investigators. However, these are far from being established in all the conditions quoted above and we know little or nothing of its capacity to do harm. If the author with his considerable medical knowledge chooses to use it on himself that is his own affair. But when a man with his following advertises a potentially dangerous drug in this way to a public who is incapable of weighing the pros and cons—for motives known only to himself—he takes a step which most medical men and other intelligent people regard as unjustified, improper and potentially harmful. E. K.

**FRANCOIS MAGENDIE.** By J. M. D. OLMSTED, Professor of Physiology, University of California. Preface by JOHN F. FULTON. Pp. 290; illustrated. New York: Schuman, 1945. Price, \$5.00.

MAGENDIE appeared on the French medical scene when France led the world, in both scientific and clinical medicine. Overshadowed by his greater pupil, Claude Bernard, his truly great contributions have tended to be overlooked. The founder of French experimental physiology, he was an early member of that great band who demanded the evidence even though at times his own studies led to unwarranted speculation. His demonstration that the anterior spinal nerve roots were motor and the posterior sensory provoked the long controversy with Charles Bell—given in detail in Dr. Olmsted's work—and led to further studies on the central nervous system, sensibility and irritability which brought him into conflict with Flourlen. One might add that the tendency to controversy among medical scientists was near its peak in the early 19th century. One also reads of Magendie's experimental study of poisons, called the beginning of experimental pharmacology, of his revolt from Bichat, of his famous *Formulary*, which went through many editions and translations, of his founding the *Journal de physiologie expérimentale*, of his studies of the cerebrospinal fluid, of his collaboration with Claude Bernard, of his efforts in the cholera epidemic, of his late "arrival" in a chair at the College de France and at a post at the Hotel Dieu and of various honors from the outerworld. We are indebted to Dr. Olmsted for this new study of a great French physiologist, and join with Dr. Fulton in the hope that others such as Brown-Séquard may later be included in the group. E. K.

**A SYNOPSIS OF MEDICINE.** By SIR HENRY LETHEBY TIDY, K.B.E., M.A., B.CH. (OXON.), F.R.C.P. (LOND.), Extra Physician to H.M. The King; Consulting Physician to St. Thomas's Hospital; Hon. Major-General, lately Consulting Physician to the British Army. Eighth Ed. Baltimore: Williams & Wilkins, 1945. Price, \$7.50.

As a *multum in parvo* ready reference desk book, Tidy's Synopsis offers an extraordinary amount of pertinent information in readily available form. The consistent use of various kinds and sizes of type, and a reasonable constancy in the order of presentation (etiology, morbid anatomy, symptoms, progress, termination, diagnosis, treatment, with occasional historical notes) considerably increase "availability," and so are especially desirable in books of this kind. This availability is further supplemented by a really adequate index of 71 pages, in small, but legible type. This edition contains the expected number of new articles, amplifications, and revisions that medical progress has necessitated. These are enumerated in the Preface. This should be read also as an indication of the wisdom that has guided the selection of items to be included and to illustrate excellent phraseology, which is apparent even in the restricted circumstances of a work of this kind. The book has already found its place on the surface of the Reviewer's desk.

E. K.

## NEW BOOKS

**Men Under Stress.** By LT. COL. ROY R. GRINKER, M.C., and MAJOR JOHN P. SPIEGEL, M.C., Army Air Forces. Pp. 484. Phila.: Blakiston, 1945. Price, \$5.00. (Reviewed on page 277.)

**Science in Progress.** Fourth Series. Edited by GEORGE A. BAITSELL. 11 Contributors. Pp. 331; 106 figs. New Haven: Yale Univ. Press, 1945. Price, \$3.00.

THE 18th anniversary issue, Vol. I, 1945, of the *Harofe Hai'vi* (*The Hebrew Medical Journal*), edited by Moses Einhorn, M.D., is a special issue dedicated to the late Henrietta Szold, distinguished humanist and Zionist who interested American Jewish womanhood in Hadassah, a great organization responsible for the medical and sanitary installations in Palestine. Since 1939 Hadassah has cooperated to the maximum with the Medical Military Forces stationed in Palestine and Near East. Special courses and clinical conferences on tropical and subtropical diseases, war surgery, typhus fever, malnutrition, etc., have been made available at the Rothschild-Hadassah-University Hospital. In addition, Hadassah's Malaria Control Service is said to have rendered Palestine the only country in this part of the world in which this infectious disease is of minor significance as a factor in troop morbidity.

**Hayfever Plants.** Their Appearance, Distribution, Time of Flowering, and Their Role in Hayfever, With Special Reference to North America. By ROGER P. WODEHOUSE, Ph.D., Associate Director of Research in Allergy, Lederle Laboratories, Pearl River, N. Y. Pp. 245; various figs. and tables. Waltham, Mass.: Chronica Botanica Co.; New York City: G. E. Stechert & Co., 1945. Price, \$4.75.

**A Handbook of Psychiatry.** By LOUIS J. KARNOSH, B.S., Sc.D., M.D., Associate Clinical Professor of Nervous Diseases, School of Medicine, Western Reserve Univ.; Director of Neuropsychiatry, City Hospital, Cleveland. With the collaboration of EDWARD M. ZUCKER, A.B., M.D., Clinical Instructor in Nervous Diseases, Western Reserve School of Medicine; Associate in Neuropsychiatry at Cleveland City Hospital. Pp. 302; 38 figs. St. Louis: Mosby, 1945. Price, \$4.50.

**Thoughts, Deeds and Human Happiness.** By K. W. MONSARRAT. Pp. 123. London, England: Hodder & Stoughton, 1944. Price, 7/6 (\$1.50).

**Trabalhos do Departamento de Anatomia Patologica** (25 reprints). Faculdade de Medicina da Universidade de São Paulo. Volumes XVI-XVII-XVIII. DIRETOR PROF. DR. LUDGERO DA CUNHA MOTTA. 1945.

## NEW EDITIONS

*An Index of Differential Diagnosis of Main Symptoms.* By Various Writers. Edited by HERBERT FRENCH, C.V.O., C.B.E., M.A., M.D. (OXON.), F.R.C.P., Consulting Physician, Guy's Hosp.; late Physician, H.M. Household. Assisted by ARTHUR H. DOUTHWAITE, M.D., F.R.C.P., Physician, Guy's Hosp.; Honorary Physician, All Saints' Hosp. for Genito-urinary Diseases. Sixth Ed. Pp. 1128: 798 ills. of which 231 are colored. Baltimore: Williams & Wilkins, 1945.

*Handbook of Practical Bacteriology.* A Guide to Bacteriological Laboratory Work. By T. J. MACKIE, C.B.E., M.D., D.P.H., Professor of Bacteriology, Univ. of Edinburgh; Honorary Bacteriologist to the Royal Infirmary, Edinburgh; and J. E. MCCARTNEY, M.D., D.Sc., Director of Research and Pathological Services, London County Council; Major, R.A.M.C. Seventh Ed. Pp. 720. Baltimore: Williams & Wilkins, 1945. Price, \$5.00.

*Clinical Atlas of Blood Diseases.* By A. PINEY, M.D., M.R.C.P., Physician, St. Mary's Hosp. for Women and Children; and STANLEY WYARD, M.D., F.R.C.P., Physician, The Royal Cancer Hosp., London, and Princess Beatrice Hosp. Sixth Ed. Pp. 137; with 48 ills., 45 in color. Phila.: Blakiston, 1945. Price, \$5.00.

*Refraction of the Eye.* By ALFRED COWAN, M.D., Professor of Ophthalmology, Graduate School of Medicine, Univ. of Pennsylvania; Attending Ophthalmologist, Philadelphia General Hosp.; Consulting Ophthalmologist, Council for the Blind and Supervising Ophthalmologist of the Dept. of Public Assistance, Commonwealth of Pennsylvania. Second Ed. Pp. 278; 172 engravings and 3 colored plates. Phila.: Lea & Febiger, 1945. Price, \$4.75

## CORRECTION

In Capt. E. R. Movitt's article "Spontaneous Pneumothorax as a Complication of Pneumonia in Adults" in our May 1945 number under the report of cases, Case 2, fourth paragraph; the dosage of Cedilanid should be as follows: "Six cc. of *Cedilanid* (1.2 mg.)"

## NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMHAAER, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles, arranged alphabetically according to the name of the first author and should be complete that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

For the balance of the war, 150 REPRINTS will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150.

# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

SEPTEMBER, 1945

## ORIGINAL ARTICLES

### ADRENALIN ADMINISTRATION IN PERSISTENT ANXIETY STATES

By D. EWEN CAMERON, M.D.

PROFESSOR OF PSYCHIATRY, MC GILL UNIVERSITY  
MONTREAL, QUEBEC

*EXISTING forms of therapy do not adequately control certain of the anxiety states. These resistant cases fall into 3 groups: (1) a number of cases in which a severe catastrophic experience results in an anxiety state which shows no tendency to clear up with the passage of time; (2) a group in which the anxiety symptoms appear as a consequence of long-continued exposure to a difficult and trying situation, such as is represented by battle experience or by conflict situations in civilian life in which the anxiety symptoms do not subside on removal from danger or on termination of the conflict situation; (3) a group in which no conflict has been present and in which there has been no exposure to danger but where the individual has had to work at high tension for prolonged periods, in industry or in the office. Similar states are appearing in housewives, overburdened with domestic duties and in children for whom recreational facilities have been sharply curtailed by the war.*

While removal of these workers from the stress-producing situation results in an abatement of symptoms in a number of cases, in many others, especially where the individual has been allowed to remain under pressure for weeks or months after symptoms have appeared, there is little or no improvement.

It is in respect to these 3 groups that our methods have proved unsatisfactory. It is important to note that in these groups the primary causes are no longer operative. It is equally important to bear in mind that our psychotherapeutic methods are almost exclusively directed to dealing with the primary causes—hence their ineffectiveness. In these cases it would appear that through long stress the individual's tendency to develop tension has become so augmented—both with regard to the ease with which the reaction is elicited and with regard to its intensity—as to make small hour to hour stresses of daily living, formerly barely noticed, now, through the repeated stimulation of the over-responsive individual, sufficient to perpetuate his



symptoms. In other words, his anxiety state has now become autonomous (Cameron<sup>3a</sup>). In medicine, our attempts to deal with undesirable responses have been, to a considerable extent, limited to dealing with primary causes. We have largely ignored the possibility of the existence of sequences which could no longer be dealt with through attacking the primary causes (Cameron<sup>3b</sup>). Hence the principles of dealing with an autonomous reaction have never been clearly worked out. In our earlier attempts to work with these conditions we based our approach on the hypothesis that if the autonomous reaction is to be perpetuated it must be called into action at frequent intervals. Consequently we directed our therapeutic efforts at preventing its avocation for an extended period of time. Some degree of success was obtained.

In the present approach to the problem we have attempted to break up the autonomous reaction by decreasing the reactivity of the individual. To achieve this we have explored the possibility of desensitizing him to adrenalin. The literature on the matter is scanty and confusing. An increased reactivity to adrenalin has been shown to exist in patients suffering from anxiety states by Maranon,<sup>8</sup> Baskova,<sup>2</sup> Richter,<sup>11</sup> Thorley.<sup>14</sup>

There is, however, little established information concerning the extent to which the reaction of the individual to the injection of adrenalin can be modified by repetition.

Repeated administration of adrenalin in animals has failed to produce any reduction in the capacity of the drug to raise the blood sugar levels (Pollak,<sup>9</sup> Affleck,<sup>1</sup> Samson and Jacobs<sup>13</sup>). The last 2 workers noted a drop below the initial level on termination of prolonged intravenous administration.

In the majority, interruption of adrenalin administration was followed by a marked drop in the blood sugar level, which slowly returned to normal. They suggest that the fall might be due to the action of the depleted liver in picking up sugar from the blood.

In animals prolonged intravenous administration is reported to result, on termination of the administration, in a drop in blood pressure below the initial level (Prohaska *et al.*,<sup>10</sup> Herman *et al.*<sup>5</sup>). Lewis and Barman<sup>7</sup> administered 1 cc. of 1/1000 adrenalin hydrochloride intravenously in dogs 3 or 4 times weekly. There was no tendency on the part of the blood pressure rises to decrease. It was noted that the dog was under chloral hydrate and atropin at the time of injection. In man, prolonged intravenous administration also resulted in a drop in the blood pressure below the initial level (Baudouin and Benard,<sup>3a</sup> 1935; Koehler *et al.*<sup>6</sup>). Rudolf (1938), after injection of 0.29 to 0.59 mg. adrenalin subcutaneously in 7 patients suffering from general paresis, found that the blood pressure rise produced on giving a second injection at intervals of 7 to 36 days, was lower than on the first occasion. It is not clear how far this was due to the patient having become accustomed to the psychologic situation represented by the injection.

Goodman and Gilman<sup>4</sup> reported that a tolerance to adrenalin, at

least with respect to its anti-spasmodic effect, may be established so that in those suffering from bronchial asthma, the amount of adrenalin administered may be progressively increased.

**Procedure.** Two methods of administration have been used, intramuscular and intravenous. The earlier cases were all treated by the intramuscular method. Before the commencement of treatment the reaction of the individual to a standard intravenous injection of adrenalin (0.01 mg.) was recorded.

Following this, intramuscular treatment was started by injecting 0.5 cc. 1/1000 adrenalin hydrochloride into the deltoid. Treatment of the earlier stages was often carried out twice daily. Most ambulant patients found this too intensive and as the dosage was increased the frequency was dropped to once daily. The dosage varied to some extent with the size of the patient and with the degree of tolerance established. The maximum single dose was 2.25 cc. The average dose lay between 1 and 1.5 cc.

As the patient improved, the frequency of dosage was reduced, first to 3 times weekly, then to once weekly, and, finally, to once every 2 or 4 weeks. This method has the advantage of being time-saving for the physicians, though it is necessary that the patient, if ambulant, should rest under observation for at least 1 hour after injection.

It has the following disadvantages: (a) There is some pain due to local pressure when larger doses are used.

(b) Absorption occasionally occurs with undue rapidity. Under such circumstances, rises in blood pressure may occur. On one occasion the pressure rose to 234/96 5 minutes after the injection of 1 cc. intramuscularly. Very severe headache lasting 8 minutes occurred. On 5 occasions, 3 in the same patient, severe headaches lasting 10 to 20 minutes occurred and in 2 patients there was some precordial pain and cardiac irregularity.

(c) The patient may remain tense and conscious of the effects of the injection for several hours.

The intravenous method was worked out in part to meet these objections and, in part, in an attempt to shorten the period of treatment. (Average about 3 months.) This method consists very simply in setting up a normal saline intravenous flow; placing a 3-way stopcock immediately behind the needle (preferably 22 gauge). Resting (30 min.) pulses and blood pressures are recorded. Adrenalin is administered through the stopcock each 10 minutes for 4 injections. Pallor, tremor, respiration, quality of pulse and patient's subjective account are recorded. The pulse is taken, commencing 40 seconds after administration, over a period of 20 seconds. The blood pressure is determined at the 90th second after the adrenalin has been run in. Pulse and blood pressure are again recorded at the 10th minute after injection. The initial dose used is 0.01 mg. The strength is gradually raised as the patient's reaction diminishes. The bulk of the injection, namely 1 cc., and the speed of injection, 1 second, are held constant. Treatments may be given daily—most commonly thrice weekly. As improvement takes place treatment is tapered off, as in the case of the intramuscular method. No untoward effects are noted; the patient has no continuing tension or other after-effects of the drug. Slight cardiac irregularities, lasting less than 1 minute, have been noted during injection. On occasion, after several weeks' treatment, fatigue on exertion was recorded, but this has been transitory.

In certain particularly apprehensive patients it is desirable to administer veronal,  $2\frac{1}{2}$  gr., t.i.d., in order to minimize the reactivity of their anxiety between treatments.

**Selection of Cases.** Only those patients should be treated in whom the anxiety state has become autonomous. Certain of our failures appear to be attributable to the fact that there was a continuing conflict situation or other current cause for the production of anxiety. Those patients in whom obsessive thinking is present do not, as a rule, do so well. We have had no occasion, as yet, to eliminate patients on physical grounds. Two patients have been treated who had had coronary occlusions over a year prior, and 1 patient was treated who had an initial blood pressure of 168/96.

**Results.** Treatment was completed in 19 cases. In 9 of the 13 in whom treatment was carried out for more than 30 days, good results were obtained, the symptoms greatly subsided or disappeared entirely and the patients were able to return to their usual occupations. The maximum period of treatment was  $5\frac{1}{2}$  months. There is some indication that the intravenous administration may shorten the period of treatment by 4 to 6 weeks. The average period of treatment was about 3 months. In 4 of these 13 patients treated for more than 30 days, transitory improvement or none at all was attained.

In the 6 cases where treatment was carried out for less than 30 days, no lasting good results were attained. Transitory improvement of good degree was attained in 3. This lasted less than 1 month. In the remaining 3 no favorable results were noted. In the 19 cases there was no evidence of the patients' reaction being adversely affected by treatment.

The immediate effects of the administration of adrenalin are already well known. In the present series it is to be noted that the emphasis by the patient was upon those symptoms which constituted the patient's customary anxiety pattern (Cameron<sup>3c</sup>)—palpitation, dyspnea, choking sensations or general increase in tension. There tended to be fleeting reactivation lasting for a few hours in the case of the intramuscular injection and a few minutes in the case of the intravenous injection of the patient's usual anxiety pattern.

As the tensional and anxiety symptoms produced by the intravenous administration of adrenalin disappeared, flushing of the face sometimes sets in, the extremities become warmer after 5 or 6 minutes, the patient stated that he felt relaxed and in several instances drowsiness and actual sleep supervened. This latter, however, first set in later in treatment, the earliest being after the 7th treatment day.

From the pulse and blood pressure response to a single injection (Table 1), it will be seen that the stimulating effect of the injection entirely disappeared by at least the 8th minute. We selected 10 minute intervals between injections as preventing any additive effects.

TABLE 1.—INJECTION OF 0.01 MG. ADRENALIN HYDROCHLORIDE I/V

	B.P.	P.	Remarks
Before injection	130/78	94	Reaction started in 24 sec. Counting of pulse started at 40 sec.
After injection:			ing of pulse started at 40 sec., lasted until 60 sec., when B.P. was taken at the 90th sec. after injection.
1 min. . . .	150/80	120	
2 " . . . .	142/74	105	
3 " . . . .	134/74	100	
4 " . . . .	132/74	93	
5 " . . . .	134/74	93	Note. Some trembling of thumb was noted at 2 min., lasted about 3 min. Patient was apprehensive for about 4 min., complained of her heart thumping, hand perspiration.
6 " . . . .	128/74	94	
7 " . . . .	126/76	96	
8 " . . . .	128/74	94	
9 " . . . .	128/74	90	
10 " . . . .	126/74	93	

The response of the blood pressure and pulse during the course of the single treatment period are shown in Tables 2 and 3. The former is the more typical. It is to be remembered, however, that patients tend to respond to adrenalin in terms of their customary pattern of

response to anxiety; and, in some patients in whom the cardiovascular pattern is not prominent, little or no change in pulse and blood pressure levels are found. The patient shown in Table 3 represents over-dosage. Extrasystoles were experienced during this treatment and for a few days thereafter the patient had some slight feeling of oppression on the precordium which disappeared with decreased dosage.

TABLE 2.—RESPONSE OF PULSE RATE AND BLOOD PRESSURE TO ADRENALIN INJECTION DURING A SINGLE TREATMENT PERIOD

	Time initial		Amount 0.04 mg.	B.P. 130/74	P. 82
1st inj.:	1 min.	. . .		188/78	85
	10 "	. . .		116/76	75
2nd inj.:	1 "	. . .		190/90	96
	10 "	. . .		118/68	78
3rd inj.:	1 "	. . .		190/90	105
	10 "	. . .		116/60	80
4th inj.:	1 "	. . .		194/86	93
	10 "	. . .		112/74	68

TABLE 3.—RESPONSE OF PULSE RATE AND BLOOD PRESSURE TO ADRENALIN INJECTION DURING A SINGLE TREATMENT PERIOD

	Time initial		Amount 0.05 mg.	B.P. 124/58	P. 87
1st inj.:	1 min.	. . .		156/72	87
	10 "	. . .		102/52	86*
2nd inj.:	1 "	. . .		152/84	82
	10 "	. . .		110/60	96
3rd inj.:	1 "	. . .		154/70	75
	10 "	. . .		106/62	93
4th inj.:	1 "	. . .		144/74	72
	10 "	. . .		110/70	105

\* Extrasystoles.

**Tolerance Acquired.** The maximum increase in intravenous dosage which has been achieved is sixfold. This was attained in 30 days in a patient who received treatment 6 days a week. Fourfold increase (from 0.01 to 0.04 mg.) is customarily obtained after about 4 to 5 weeks on the basis of treatment 3 times a week. Progressive tolerance, as recorded by the pulse and blood pressure is shown in Table 4. Tolerance is, however, rarely best shown by the blood pressure or the pulse. It is more easily seen in the progressive subsidence of pallor, tremor, dyspnea and in the patient's own statement that succeeding injections seem milder.

**Cases.** CASE 1. A 36 year old married man came on June 2, 1943, complaining of tension and anxiety of such severity that he was unable to work.

The patient, who had, since his earliest years, tended to worry, to be unduly conscientious and to have difficulty in making adjustments, grew considerably more anxious after entering the army in March 1943. He was admitted to an army hospital because of anxiety and severe tremor. The latter was so marked that he was diagnosed as suffering from paralysis agitans and was discharged in May 1943.

On examination considerable tremor of the hands was noted. No evidence of encephalitis lethargica was found. The patient complained of feeling tightened up, of being restless; there were drawing sensations in the shoulders

and aching in the back of the neck; the voice was quavering. The patient stated that when he became especially anxious there was a generalized tremor. He had difficulty in concentrating and making decisions and in taking an interest in things; he could not go into crowds, was more sensitive and was, at times, so depressed and anxious that he thought of suicide.

TABLE 4.—RESPONSE OF PULSE RATE AND BLOOD PRESSURE TO INJECTION OF 0.01 MG. ADRENALIN HYDROCHLORIDE INTRAVENOUSLY AT VARIOUS STAGES IN TREATMENT

Date 1943	Resting		1st min.		10th min.		Remarks
	B.P.	P.	B.P.	P.	B.P.	P.	
July 11	134/80	104	148/82	143	124/80	93	0.04 cc. adrenalin given b.i.d. July 11 until July 15, 1943; then 0.7 cc. b.i.d. until July 21; 0.4 cc. b.i.d. until Aug. 2; then 1 cc. once daily Veronal, 2½ gr., b.i.d. started July 25, 1944.
July 21	118/80	92	128/82	114	116/70	79	
Aug. 20	114/76	65	136/76	104	110/72	62	
Sept. 19	114/72	77	130/74	96	106/72	72	

His resting blood pressure was 154/94; his pulse 77. In response to an intravenous injection of 0.01 mg. adrenalin hydrochloride, his pressure rose at the end of 1 minute to 166/96; his pulse to 90; he had a feeling of weakness, his heart pounded and felt as "though it would burst." At 10 minutes the readings were 106/82 and 79. He was started on intravenous intramuscular adrenalin injection and was put on veronal, 2½ gr., t.i.d. On July 4, 1943, the standard dose (0.01 mg.) of adrenalin was again injected. Resting readings were 122/76 and 67—1 minute readings were 132/82 and 81 and 10 minute readings were 114/70 and 66. At this time the patient was better, wanted to meet people, was planning to get back to work. On Aug. 27, 1943, his reactions to the test dose were: resting levels 126/76, 64; 1st minute, 132/80, 87; 10 minute, 118/80, 67. At this time the patient had been back to work as a machine operator, working 8 hours daily. He was still apt to get a little shaken; would wake 4 or 5 times nightly but go off to sleep again. Drowsy feelings and fatigue were gone. There was still some quavering of the voice and there was still some difficulty in concentrating. He was able to go to shows but avoided other crowds; was working daily. His dose of veronal had been reduced to once daily. He had been getting 2 cc. of adrenalin intramuscularly daily—this was cut to 1 cc. after a series of 3 headaches. In September the patient was still better, was working steadily. He had occasional shaking of the hands if he was under a strain; his appetite was good, and he gained about 7 pounds in about 2 months. He was then receiving 1 cc. of adrenalin twice weekly.

CASE 2. A 32 year old married woman who came on Nov. 22, 1943, with complaints that about 16 months prior she began to suffer from periods of anxiety, palpitation and vomiting.

These had set in about 2 months after the birth of her child and coincided with a period of considerable stress due to the lack of domestic help. The first period had lasted about 2 months. The present period had set in about 2½ months prior to examination. When seen she complained of daily vomiting before her breakfast, sometimes before all meals, palpitation was almost continuous and pounding in nature; she required nightly sedatives, could not concentrate well, and had most considerable anxiety and some depression. The patient was inclined to ascribe her difficulties to long feelings of inadequacy and to her unwillingness to settle down to a domestic life. Prior to the birth of her child she had carried on a part-time bookkeeping job. Consequently, the patient was treated psychotherapeutically until March 28, 1944. No progress was made and the vomiting spells had to be controlled from time to time by sodium amytal, given before meals, and by insulin. On March 28 it was decided to institute intravenous adrenalin treatment. Her reaction

to 0.005 mg. was: resting readings, 106/60, 75; 1st minute, 110/88, 93; and 10th minute, 112/72, 68. Treatment was given 3 times weekly, 4 injections being given during each treatment. On April 6 her dose was raised to 0.01 mg. and was raised steadily, reaching 0.02 on April 13; 0.03 on April 24; and 0.04 on June 7. Slow improvement took place. On April 13 veronal,  $2\frac{1}{2}$  gr., t.i.d., which she had been taking for several months, was reduced to twice daily as she was reported feeling more relaxed. She said she felt tired after going home following on treatment and noted that she had become rather short of breath since the treatment started. That statement, together with the fact that she had a feeling of constriction in the chest and occasional pain in the left side immediately after injection, resulted in the strength of the dose being raised slowly. On April 11, for the first time, the patient began to get drowsy. About the 6th minute after injection on subsequent occasions she went to sleep during the treatment. On April 28 she dropped another of her veronal doses; her vomiting had been growing steadily less, but, on occasion, as in early May when she had difficulties with domestic help, it returned. At this time she stated that she looked forward to the treatment days as she could be sure of some hours of relaxation thereafter. It was noted that her reactivity to a given dose of adrenalin was greater during menstrual periods. On June 12 she reported that she had had no vomiting for 3 weeks, she had taken no sedatives at night nor any veronal for 3 or 4 weeks. She was still taking sodium amytal,  $1\frac{1}{2}$  gr., before her noon meal. Her concentration was much better; there was little palpitation; mild anxiety was still present for a short period in the morning. She was now able to go out socially; could attend movies, something which was impossible before treatment. Her resting readings were 104/62 and 73. It is to be noted that this patient's anxiety pattern was dominantly gastro-intestinal; and, though she had reported palpitation, we had never actually found tachycardia. In mid-June she went to the country for the summer and in early August she was reported by her husband as being in good health, eating well, gaining in weight, and experiencing no anxiety. She was using no sedatives.

**Discussion.** That tolerance to increasing amounts of adrenalin can be established appears to be certain. It would seem that this process is complex and comprised of both a lessened reactivity of the mechanisms which ordinarily react to adrenalin and also of an increased vagal activity. The first is shown in the reduction of such symptoms as pallor, tremor and dyspnea. The second, namely, increased vagal activity, is suggested by the increase, after repeated injections, of the flushing of the face, drowsiness and feelings of relaxation. The basis for the progressive lowering of the resting blood pressure and pulse and the decreased pulse and blood pressure rise to a standard dose are less easy to designate as being due primarily to a decreased reactivity of the adrenal sympathetic mechanisms or to an increase in the compensatory action of the vagal system.

As can be seen from the record, this therapy is not effective in all instances. It appears to be most successful where the anxiety state is truly autonomous and where the anxiety has not become organized into fixed obsessive symptoms.

In conclusion, it may be necessary to point out that the fact that a physiologic method has been used to treat these cases of autonomous anxiety and the fact that it appears to have been successful in a certain number of instances does not, in any way, imply that the initial disturbance was at the physiologic level. Save for a very few instances occurring primarily in the investigative field where anxiety can be

produced by physiologic agents, one may say that anxiety is essentially an accompaniment of the adjustment of the individual to his environment.

**Summary.** 1. Patients suffering from certain types of anxiety state do not respond well to the existing forms of therapy.

2. This is particularly true where the anxiety states have become autonomous.

3. In such cases overactivity of the adrenal sympathetic nervous system appears to be established.

4. Repeated adrenalin administration tends to reduce this overactivity; with reduction in overactivity the patient's symptoms abate.

#### REFERENCES

1. AFFLECK, A. M.: Affect of Long Continued Administration of Adrenalin, *J. Pharm. and Exp. Ther.*, **36**, 301, 1939.
2. BASKOVA, E.: Der Zustand des Vegetativen Nervensystems bei klimakterischen Neurosen, *J. Neuropat. i. psychiat.*, **20**, 185, 1927.
- 2a. BAUDOUIN, A., and BENARD, H.: Injections Intraveneuses lentes et continues d'Adrenaline chez l'Homme. *Compt. rend. Soc. d. biol.*, **191**, 474, 1935.
3. CAMERON, D. E.: (a) Autonomy in Anxiety, *Psychiat. Quart.*, **18**, 53, 1944; (b) Types of Sequence in Human Behavior, *Psychiat. Quart.*, **18**, 490, 1944; (c) Observations on the Patterns of Anxiety, *Am. J. Psychiat.*, **101**, 36, 1944.
4. GOODMAN and GILMAN: *The Pharmacological Basis of Therapeutics*, New York, Macmillan, p. 415, 1941.
5. HERMAN, H., JOURDAN, F., et al.: Sur les effets de l'injection intraveineuse continue d'adrenaline, *Compt. rend. Soc. d. biol.*, **130**, 952, 1939.
6. KOEHLER, A. E., MARSH, N., and HILL, E.: The Effect of Epinephrine Injected Intravenously at a Constant Rate in Normal and Hypertensive Cases, *J. Biol. Chem.*, **119**, lix, 1937.
7. LEWIS, J. S., and BARMAN, J. M.: Affects du traitement prolongé par l'adrenaline est le sang de la veine surrenale, *Compt. rend. Soc. d. biol.*, **130**, 172, 1939.
8. MARANON, G.: Emotive Action of Epinephrine, *Rev. franc. d'endocrinol.*, **2**, 301, 1924.
9. POLLAK, L.: Zur Frage der Adrenalingewohnung, *Ztschr. f. physiol. Chem.*, **68**, 69, 1910.
10. PROHASKA, J. VAN, HARNS, H. P., and DRAGSTEDT, L. R.: Epinephrine Hypertension: The Effect of Continuous Intravenous Injection of Epinephrine on the Blood Pressure, *Trans. Am. Surg. Assn.*, **55**, 369, 1937.
11. RICHTER, D.: The Action of Adrenalin in Anxiety, *Proc. Roy. Soc. Med.*, **33**, 615, 1940.
12. RUDOLF, G. DE M.: Unusual Results Following the Injection of Epinephrine, *Endocrinology*, **23**, 366, 1938.
13. SAMSON, P. C., and JACOBS, H. R. D.: Some Clinical Effects From Constant Intravenous Epinephrine Injection in Dogs, *Am. J. Physiol.*, **99**, 453, 1931-1932.
14. THORLEY, A. S.: Action of Adrenalin in Neurotics, *J. Neurol. and Psychiat.*, **5**, 14, 1942.

### EOSINOPHILIC LUNG (TROPICAL EOSINOPHILIA)

BY LT. COL. PHILIP J. HODES, M.C., A.U.S.

AND

COL. FRANCIS C. WOOD, M.C., A.U.S.

20TH GENERAL HOSPITAL A.P.O. 689, NEW YORK, N. Y.

Eosinophilic lung (tropical eosinophilia, pseudotuberculosis associated with eosinophilia) is a disease characterized by bronchopulmonary changes and eosinophilia. Although not described in the literature until recently, it occurs often enough in India to be a problem and

has been reported in Australia and Singapore.<sup>7</sup> Since the disease is known to develop in Europeans,<sup>1,7</sup> it may also involve Americans (troops) returning from the Orient. It seems important therefore for physicians in the Western Hemisphere to familiarize themselves with the manifestations of eosinophilic lung. The purpose of this communication is to review the literature, and to describe the clinical and roentgenologic findings in 2 patients with the disease.

**Review of Literature.** In 1940, Frimodt-Moller and Barton first described "a pseudo-tuberculous condition associated with eosinophilia" in the *Indian Medical Gazette*.<sup>3</sup> They collected 175 cases from a tuberculosis sanatorium in Madanapolle, South India, who showed eosinophilic leukocytosis, usually associated with cough and fever. Roentgenograms of the chest showed "evenly distributed extensive mottling of small nodular shadows over both lung fields with increased linear markings." After careful study these authors concluded that the syndrome was not explainable on a basis of tuberculosis, syphilis, heart disease, Loeffler's syndrome, or any known clinical entity.

In 1943, Weingarten reported 81 patients with tropical eosinophilia (eosinophilic lung), most of whom lived along the western seacoast of India (Bombay, Cujerat, Kathiawar, Malabar and Coromandel coasts<sup>8</sup>). About the same time Simeons reviewed his findings in 35 patients collected in Bombay during a period of 9 years.<sup>5</sup> More recently Treu described the disease in Calcutta, reporting its occurrence in patients from Raniganj, Bihar and Singapore.<sup>6,7</sup>

(a) **Etiology.** Nothing definite is known concerning the etiology of eosinophilic lung. Weingarten is convinced that climatic and geographic factors are important. He has never seen a patient with the disease who had always lived in a dry climate of the type found in northwest Rajputana. Moreover, all of his patients with eosinophilic lung lived near the sea. The asthmatic manifestations of the disease and its eosinophilia suggest an allergic factor, perhaps in response to parasitic allergens, but no definite facts have been discovered to support this suggestion. Carter, Wedd and D'Abrera, working in Ceylon,<sup>2</sup> identified the cheese-mite (*Tyroglyphus*) and some of its near relatives in the sputum of patients with eosinophilic lung, and attributed the disease to them. However the etiologic significance of mites in this condition still remains to be established.

The disease has no seasonal incidence. Race and age do not seem to be factors. It has been reported in a child of 7 and an adult of 52. All classes of society are affected, strict vegetarians and meat eaters being equally vulnerable. It is not related to the use of alcohol.

(b) **Clinical Findings.** In most cases the disease is ushered in with lassitude, loss of appetite and fever which rises to 100° to 101° in the evening. During the 2nd week of the illness, the patient usually develops a dry hacking cough which seems to be worse at night. As the malady progresses, the cough becomes more severe and paroxysmal, eventually interfering with sleep. Wheezing and expiratory dyspnea develop. Many have the symptoms of asthmatic bronchitis. Some have severe paroxysms of asthma requiring epinephrine. In rare



instances an explosive asthmatic attack may be the first sign of the patient's illness. Those who suffer considerable nocturnal distress not infrequently remain comfortable and comparatively free from symptoms during the day. After several weeks the fever subsides, weakness gradually disappears, and there is no further loss of weight. The bronchopulmonary symptoms, however, usually persist and become chronic if treatment is not instituted.

Whereas fever and bronchopulmonary complaints are usually present in eosinophilic lung, there are patients in whom these phenomena are not prominent. Fever may be entirely lacking. The patient may have no respiratory symptoms even though pulmonary changes are evident in roentgenograms.<sup>8</sup> Treu believes that the only phenomena which are consistently present in tropical eosinophilia are the blood picture and the clinical response to specific therapy.<sup>7</sup>

In the mild cases, physical examination reveals slight hyperresonance of the chest. The expiratory sounds are prolonged. Sibilant and sonorous ronchi usually are present, with occasional crepitant râles at the bases. Physical signs during the acute respiratory seizures are those of true bronchial asthma. Expectoration is usually scanty, glassy and tenacious. On microscopic examination the sputum often contains clumps of eosinophils and rarely Charcot-Leyden crystals or Curschmann spirals. The common bronchopulmonary bacteria are often found on culture. During the febrile period of the illness the spleen is moderately enlarged in at least half of the cases, extending 3 to 5 cm. below the costal margin. It is usually smooth, firm and not tender.

The most striking feature of eosinophilic lung is the massive eosinophilia. The total white count is usually above 20,000 and often above 40,000. Much higher figures are by no means uncommon, in some instances reaching 70,000 to 80,000. The elevated count is primarily due to an increase in the number of eosinophils which may constitute 92% of the total white cells counted. The other elements in the white blood count remain essentially unchanged. Weingarten believes the eosinophils are normal and fully mature. Simeons, however, states that their nuclei are abnormally lobulated. The red cells are usually normal. Occasionally a mild secondary anemia is observed. The sedimentation rate may be moderately accelerated. Nothing remarkable has been found in the studies of blood chemistry, urine or stools.

(c) **Roentgen Findings.** According to Weingarten, roentgenograms of the chest made at the end of the 2nd week of the febrile period reveal a distinctive mottling which is distributed throughout both lungs. The individual lesions are from 2 to 5 mm. in diameter, and have a somewhat dense center and ill-defined blurred periphery. The areas of mottling are more numerous and slightly larger in the hilar region, and more common in the bases than in the apices. Whether the primary lesion is bronchiolar or alveolar is not known. Weingarten believes the anatomic distribution of the lesions favors an alveolar origin. In his opinion, the Roentgen appearance is dependent on

bronchopneumonic infiltration of groups of alveoli.<sup>8</sup> The early stage of the disease, which is characterized radiographically by diffuse pulmonary mottling, rarely lasts more than 4 weeks. Thereafter the infiltrations regress until one can see only prominent hila and truncal markings in the films of the chest. Patients in whom the disease has been present for a long period of time rarely present the parenchymal mottling seen during the 1st weeks.<sup>7,8</sup> It is noteworthy that Treu has observed patients with clinical manifestations of eosinophilic lung in whom nothing could be demonstrated roentgenographically. Conversely, he has also found patients with Roentgen evidence of the disease who have had none of the clinical findings.

(d) **Treatment.** The present, very effective, treatment of the disease was discovered by chance. Weingarten recounts the episode as follows: "At the end of 1936, 1 patient (Case 24), already under observation, contracted syphilis, and neoarsphenamine was given. When his white cells were counted after 4 injections (0.15, 0.13, 0.45 gm. twice) they had fallen from 64,200 to 7800 and the eosinophilia had decreased from 71 to 16%. His subjective symptoms had also vanished. But it was not until 1938 that I realized that this was no coincidence; since then, cases have been systematically treated with neoarsphenamine, which proved to be a quickly acting specific. Injections are given every 4th day usually in a course of 6 (0.15, 0.3, 0.45 gm. twice or thrice)."<sup>8</sup> After the 1st 2 or 3 injections, there is a tendency for a further slight increase in the total leukocyte count as well as in the percentage of eosinophils; later they abruptly diminish, sometimes even before therapy has been completed, in other cases only after the end of the course. Clinical symptoms disappear rapidly and completely usually after the 3rd injection.

**Case Reports.** CASE 1.\* The patient, an Anglo-Indian from Calcutta, 17 years old, was first seen on Dec. 30, 1943, because of fever ( $101^{\circ}$  to  $102^{\circ}$ ), weakness and dyspnea on exertion of 2 weeks duration. There was no history of asthmatic attacks, although the patient did have a very mild cough. Physical examination revealed somewhat harsh breath sounds over the chest, but no râles were heard. The spleen was slightly enlarged. No other important physical findings were recorded. The patient's white blood count was 21,000 with 38% of eosinophils. Roentgenograms of the chest revealed the following (Fig. 1 A): The bones of the thoracic cage were negative. The trachea was in the mid-line. The heart, aorta and domes of the diaphragm were normal. Both hila were considerably increased in prominence. Distributed throughout both lungs were multiple areas of coalescent nodulation and mottling. The densities were uniformly distributed throughout both lungs from apex to base, and from the hila to the periphery. The densities were soft, irregular and tended to coalesce. The appearance was not unlike that seen in hematogenous tuberculosis or miliary metastatic malignancy.

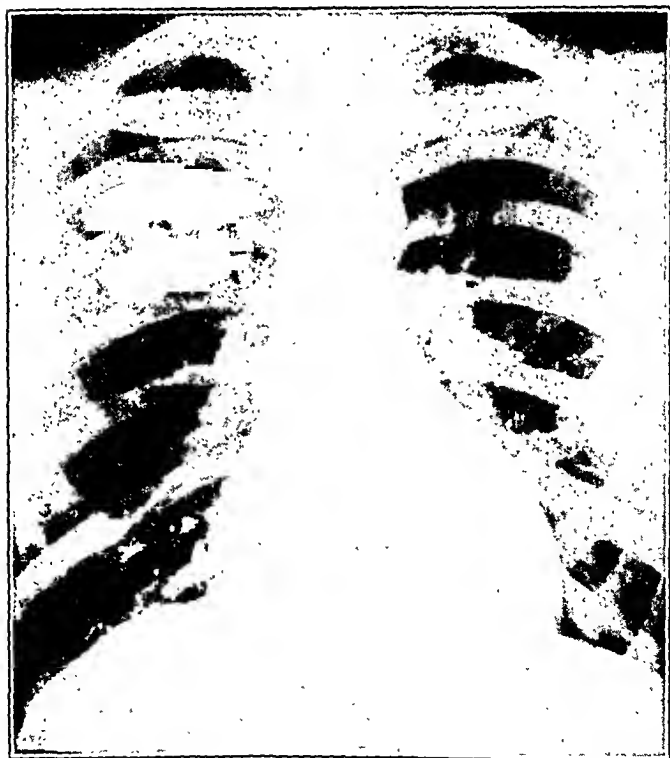
Neoarsphenamine was started on Jan. 2, 1944. During the period from January 2 to 21, the patient received 5 injections of 0.3 gm. each. Following the 2nd injection, the patient was practically well clinically.

Roentgenograms of the chest made on February 22 revealed an essentially healthy chest (Fig. 1 B). The resolution of the inflammatory lesions was as complete as in simple bronchopneumonia.

\* We are indebted to Dr. Rudolph Treu of Calcutta for this patient's clinical record and chest reproductions. This is Case 3 in Dr. Treu's paper "Pseudo-Tuberculosis of the Lungs with Eosinophilia," which will appear in the Indian Medical Gazette.<sup>7</sup>

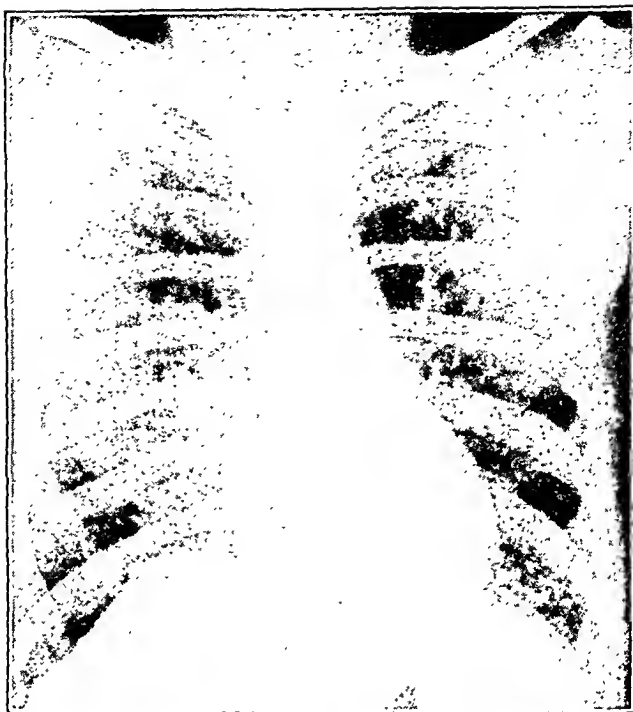


A

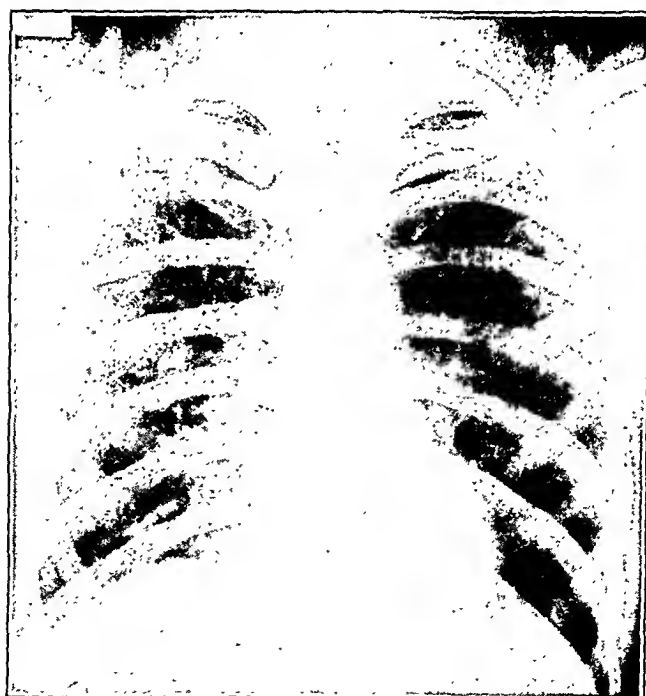


B

FIG. 1.—Eosinophilic lung. Case 1. (E.C.F.B.) A, Film of the chest made Dec. 30, 1943. Illness 2 weeks duration. Note diffuse nodulation and mottling. B, Roentgenogram made Feb. 22, 1944, when patient clinically well. Findings compatible with a healthy chest. (Courtesy of Dr. R. Treu.)



A



B

FIG. 2.—Eosinophilic lung. Case 2. A, Roentgenogram of the chest made on March 27, 1944, during the third week of the patient's illness. Note diffuse nodulation and increased prominence of the right hilum. B, Reëxamination made May 1, 1944, when patient clinically well. The Roentgen findings are compatible with a healthy chest. (Courtesy of Capt. G. L. Birnie, R.A.M.C.)

CASE 2.\* The patient, an Indian from Madras, was admitted to a British Army Hospital complaining of a dry hacking cough and daily asthmatic attacks of 3 weeks duration. His daily temperature during this period ranged from normal in the forenoon to  $100^{\circ}$  to  $101^{\circ}$  in the late afternoon. Physical examination revealed many coarse and musical râles in both lungs. The spleen was moderately enlarged. The sputum was colorless, containing mucus and many eosinophils. The red blood count was 4,700,000. The white blood count was 40,000 with 65% eosinophils, 14% polymorphonuclear leukocytes, 16% lymphocytes and 5% monocytes.

We saw this patient on March 27, 1944, just before he was treated. Roentgen examination of the chest revealed the following (Fig. 2 A): The bones of the thoracic cage were normal. The trachea was in the mid-line. The heart and aorta were normal. The right hemidiaphragm showed a nodular appearance in its medial third, which suggested a lesion in the liver. The left hemidiaphragm was normal. Both hila were increased in prominence, the right more so than the left. Distributed throughout both lung fields were innumerable small nodules which appeared to coalesce in many areas. The nodules were not sharply demarcated but seemed rather "soft" and irregular. Their appearance in no way suggested the firm, dense, well-circumscribed nodules seen in silicosis. Both lung fields were somewhat hazy, presenting a rather diffuse ground-glass appearance, through which the disseminated nodulation and mottling were seen. Most of the nodules measured from 1 to 3 mm. in diameter. The largest areas of coalescent nodulation and mottling were about 7 mm. in diameter.

The patient was treated with neoarsphenamine, receiving 0.1, 0.3, 0.45, 0.45 gm. at 3 to 5 day intervals. When we saw him again on May 1, 1944, he was symptom-free and his blood count was normal. Roentgenograms made of the chest on May 1, 1944, revealed a healthy chest (Fig. 2 B).

**Discussion.** The importance of recognizing eosinophilic lung early cannot be overemphasized because the treatment is simple and effective. The diagnosis is not difficult. It is suggested by the finding of eosinophilic leukocytosis, fever, cough, asthma and Roentgen changes in a patient who has been in India. It is confirmed by the response to arsenic. Whereas the Roentgen changes are not pathognomonic of eosinophilic lung, the possibility of its presence must be kept in mind constantly by the radiologist when confronted with a diffuse pulmonary nodulation or mottling similar to that seen in miliary tuberculosis, silicosis, aspergillosis, periarteritis nodosa, metastatic malignancy, etc.

The "eosinophilic lung" may eventually prove to be related to the "Fleeting Pulmonary Infiltration with Eosinophilia" described by Loeffler in 1936.<sup>4</sup> However, the evidence now available indicates that it is probably a separate disease entity. Patients with Loeffler's syndrome have few if any subjective findings. Occasionally there is low fever and an irritative cough. There is a slight leukocytosis (14,000); the eosinophilic percentage may reach 66%; well-developed pulmonary infiltrations are seen in roentgenograms of the chest. The chest lesions are almost always more extensive than one would anticipate from the clinical findings alone. As a rule, patients with Loeffler's syndrome are ill for only 1 or 2 weeks. The disease rarely becomes chronic like untreated eosinophilic lung, and asthmatic attacks are not reported to occur. The Roentgen appearance of the lungs also differs, in that the

\* We are indebted to Captain G. Leslie Birnie, R.A.M.C., for this patient's clinical record. The roentgenograms of this patient's chest were made in our hospital.

diffuse mottling which characterizes eosinophilic lung is uncommon in Loeffler's syndrome. In the latter, large round or irregular pulmonic lesions, unilateral or bilateral, single or multiple, which look like tuberculosis, are the rule. They appear and disappear in chest roentgenograms rapidly, frequently completing the cycle in a week. Loeffler's syndrome appears to have a seasonal frequency, being more common in July or August, which is not true of tropical eosinophilia. Furthermore, the latter disease is found in tropical monsoon regions, whereas Loeffler's syndrome appears to be a disease of temperate climate.

Our experience with eosinophilic lung is limited to a few patients whom we have seen through the kindness of other physicians. In only 1 patient did we make our own roentgenograms of the chest. One of us spent some time discussing the problem with Dr. Rudolph Treu in Calcutta, who placed all his material at our disposal, and to whom we are indebted for Case 1. Most of Dr. Treu's patients, early in the disease, revealed prominent hila and diffuse pulmonary nodulation and mottling roentgenographically. The chronic pulmonary changes of the later stages were similar to those seen radiographically in early bronchiectasis or well-established tracheobronchitis. Occasionally the films of the chest in chronic cases showed no significant abnormality.

There is nothing pathognomonic in a roentgenogram of the chest of a patient with eosinophilic lung. This condition may mimic other bronchopulmonary conditions. It is only by maintaining a high index of suspicion in all patients with diffuse pulmonary nodulation or mottling, that eosinophilic lung will be diagnosed early.

**Summary.** 1. Two cases of tropical eosinophilia (eosinophilic lung) are described, and the literature on the subject is reviewed.

2. This condition is well known in India, and may appear in America, in troops returning from the Orient.

3. The diagnosis is not difficult. The typical clinical picture consists of a pronounced eosinophilic leukocytosis in a patient with asthmatic bronchitis, fever, a palpable spleen, and Roentgen evidence of diffuse mottling and "soft" nodulation throughout both lungs.

4. Treatment with neoarsphenamine is very effective.

5. Without arsenical therapy the condition tends to persist.

#### REFERENCES

1. APLEY, J., and GRANT, G. H.: *Lancet*, p. 308, Sept. 2, 1944.
2. CARTER, H. F., WEDD, G., and D'ABRERA, V. St. F.: *Ind. Med. Gaz.*, 79, 163, 1944.
3. FRIMODT-MOLLER, C., and BARTON, R. M.: A Pseudotuberculous Condition Associated With Eosinophilia, *Ind. Med. Gaz.*, 75, 607, 1940.
4. LOEFFLER, W.: Fleeting Pulmonary Infiltration With Eosinophilia, *Schweiz. med. Wehnschr.*, 45, 1069, 1936.
5. SIMEONS, A. T. W.: Pseudo-tuberculosis of Lungs With Eosinophilia, *Ind. Med. Gaz.*, 78, 271, 1943.
6. TREU, R.: Pseudo-tuberculosis of the Lungs With Eosinophilia, *Ind. Med. Gaz.*, 78, 70, 1943.
7. TREU, R.: Pseudo-tuberculosis of the Lungs With Eosinophilia or Benign Eosinophil Leucæmia (to be published).
8. WEINGARTEN, R. J.: Tropical Eosinophilia, *Lancet*, 1, 103, 1943.

LARYNGEAL EDEMA, MYOCARDITIS AND UNEXPECTED DEATH  
(EARLY ACUTE LARYNGOTRACHEOBRONCHITIS)\*

BY OTTO SAPHIR, M.D.

CHICAGO, ILL.

(From the Department of Pathology† of the Michael Reese Hospital)

FIVE unusual instances of unexpected death occurring shortly after the sudden onset of marked respiratory difficulty and cyanosis in previously healthy children were recently observed. The course of the disease was short and dramatic. The cause of death was found to be myocarditis, which clinically had not been diagnosed. The purpose of this study is to draw attention to this unrecognized complication of a severe upper respiratory disease which probably is an early manifestation of so-called laryngotracheobronchitis. Though there are on record numerous instances of this disease, myocarditis as such has not been stressed as a cause of death. Yet unexpected and unexplained death of these patients had been repeatedly stressed. While the autopsies disclosed the nature of the disease and the cause of death, they did not shed light on the etiologic moment.

Two of the 5 children were admitted to the Sarah Morris Hospital,‡ 1 to the Chicago Memorial Hospital,‡ and the 4th to the Municipal Contagious Hospital.‡ The 5th child died in the ambulance en route to the Municipal Contagious Hospital.

**Clinical Abstracts.** CASE 1. A male, 2 years old, became suddenly ill with marked hoarseness and difficulty in respiration. He was rushed to the hospital where it was found that he had a temperature of 104°, respirations of 60 per minute, and a pulse rate of 112 to 128. He appeared cyanotic. Expiration was extremely difficult, and there was marked retraction of the chest. Intubation gave no relief. The child died suddenly,  $\frac{1}{2}$  hour after admission to the hospital. Examination for *Corynebacterium diphtheriae* proved negative.

CASE 2. The second child was a girl 11 months old. She was admitted to the hospital because of difficulty in breathing and high fever. She had had a mild cold for 3 weeks. Twelve hours before admission marked difficulty in breathing developed. On admission to the hospital the face, lips, tongue and buccal mucosa were cyanotic. The mucosa of the throat was reddened. There were short, rapid respiratory movements with marked laryngeal stridor and infrasternal retraction. The temperature varied between 100.8° and 103.8°. Respirations were 42 to 64 per minute. The child was intubated, and since difficulty in breathing persisted, a tracheotomy was performed. Some improvement followed tracheotomy, and the child was placed in an oxygen tent. However, sudden severe cyanosis developed, the child became comatose and died 16 hours after admission to the hospital. During the hospital stay the patient received, in addition to oxygen therapy, sulfadiazine, penicillin and nembutal. Cultures from the throat disclosed non-hemolytic streptococci.

CASE 3. A female, 3 years old, had been well until she suddenly complained of earache and aching in the knees and wrists; on the evening of the same day pain on swallowing was discovered, and at night she became very restless and cyanotic. On admission to the hospital, the mucosa of her lips was markedly

\* Aided by a grant from the Otto Baer Fund.

† This department is in part supported by the Michael Reese Research Foundation.

‡ For the use of the clinical records I am indebted to the Pediatric Department of Michael Reese Hospital, to Dr. G. H. Scott and to Dr. Archibald L. Hoyne, respectively.

cyanotic, and the base of the tongue and the epiglottis were severely edematous. She was given oxygen and a tracheotomy was performed. The patient died unexpectedly 2 hours after admission to the hospital. Examination of the throat for *C. diphtheriæ* gave negative results. However, non-hemolytic streptococci were isolated.

CASE 4. A 3 year old girl was well until she caught a cold about 2 weeks previously. On the day before admission to the hospital she complained of a sore throat and difficulty in breathing. The latter became worse the following morning, and the patient was rushed to the hospital as an emergency. On admission the temperature was 102.4°, pulse rate 120, and respirations 44. The child was markedly dyspneic with rapid and noisy respirations. Her face was cyanotic, and her throat was filled with mucus. The tonsils were edematous, and the mucosa covering the pharynx was fiery red.

Smears and culture from the throat for *C. diphtheriæ* gave negative results. Non-hemolytic streptococci, however, were isolated.

Shortly after admission the patient was given oxygen, sodium sulfadiazine, and penicillin. However, the breathing became more difficult, the cyanosis more severe, and the child was rushed to the operating room for tracheotomy, but death occurred just before she reached the operating room, 1 hour and 10 minutes after admission.

CASE 5. A male, 7 years and 10 months old, developed respiratory difficulties and became "blue in the face." He was rushed to Municipal Contagious Hospital but was pronounced dead on arrival.

**Autopsy Findings.** Only the more important changes will be mentioned. The gross and histologic findings in these 5 children were quite similar. There was marked redness of the mucosa of the *pharynx* and *larynx*. The outstanding change, however, was a severe edema of the submucosa of the *epiglottis* and the *pyriform sinus*. The false and true *vocal cords* were soft, red and swollen. The subglottic tissues were also reddened and so edematous that the air passage was markedly narrowed. The mucosa of the *trachea* was fiery red, but the bronchial mucosa was only moderately hyperemic. There was no evidence of an exudate within the air passage. The *lungs* on gross examination disclosed a moderate edema and foci of atelectasis, but there was no gross evidence of pneumonia.

The *hearts* of all 5 children were dilated, soft and grayish brown. The valvular apparatus was intact. The *liver* and *kidneys* were the seat of cloudy swelling. In all these instances the *thymus* was somewhat larger than normal. The mediastinal, peritoneal and retroperitoneal *lymph nodes* were also slightly enlarged and soft. The Peyer's patches and solitary lymph follicles in the lower *ileum*, however, were very prominent. In only 1 of the children were the cervical lymph nodes swollen and soft.

*Microscopic studies* proved illuminating. Outstanding changes of an inflammatory nature were found in the myocardium. The myocarditis was principally interstitial in distribution, and most of the inflammatory cells were lymphocytes. Rarely neutrophils were encountered. A number of regions of the myocardium were not involved, and in 2 instances 10 blocks of the myocardium had to be sectioned before evidence of the myocarditis was found. This detailed study was undertaken because the history as well as the lesion in the larynx were identical to those in other instances in which myocarditis was found. Myocarditis was anticipated and was therefore carefully sought. The right ventricle of the heart was usually more severely affected than the left. The subendocardial regions appeared to be especially frequently involved.

The *lungs* in 3 of the 5 instances disclosed on microscopic examination early bronchopneumonia which was not recognized grossly. The larynx and trachea were the seat of a marked edema. Often the submucosa was also infiltrated with lymphocytes, neutrophils and monocytes. The severity of the inflammation varied somewhat. It is noteworthy that there was no exudate encountered covering the mucosa. Only once was the mucosa involved, and small foci of necrosis were encountered. Cultures for the presence of *C. diphtheriæ* were taken in 4 children, but their examination yielded negative results.



**Comment.** The outstanding gross and histologic findings in all instances were edema of the epiglottis, vocal cords and subglottic region, and myocarditis.

These 5 children who had been relatively well suddenly developed severe respiratory difficulties with marked cyanosis. The respiratory difficulties were sometimes so marked as to suggest the presence of a foreign body in the respiratory tract and to indicate tracheotomy which was performed on 2 children. One child died just before a contemplated tracheotomy. All children with the exception of the one who died *en route* to the hospital had been intubated. The cause of the respiratory difficulties proved to be a severe edema of the subglottic region. This was obviously part of an inflammatory exudate, serum constituting the predominating component, since other evidence

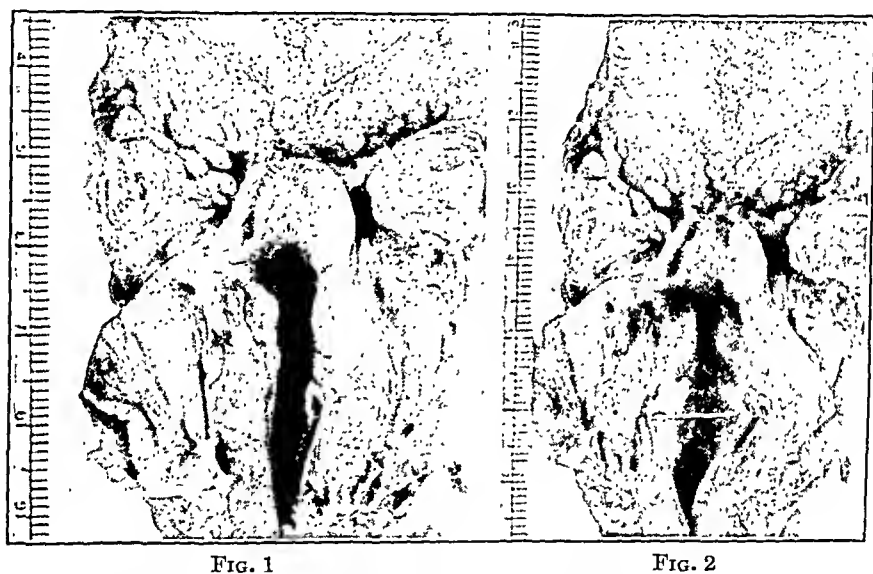


FIG. 1

FIG. 2

FIG. 1.—Epiglottis and larynx (closed). Note the marked edema of the epiglottis.  
FIG. 2.—Larynx open. Note the edema of the vocal cord and epiglottis.

of inflammation of varying degree was encountered on histologic examination. *C. diphtheriae* as the cause of the inflammation could definitely be ruled out since neither fibrin nor foci of necrosis were consistently present. Smears and cultures were negative for *C. diphtheriae*. It seems probable that this lesion should be classified as a very early manifestation of so-called laryngotracheobronchitis. The literature on this subject is reviewed in the more recent publication of MacCready,<sup>1</sup> Orton *et al.*,<sup>2</sup> Brennemann *et al.*,<sup>3</sup> and Smith.<sup>4</sup> Quite characteristic of this condition is the more or less sudden onset of the respiratory distress and the unexpected and "sudden" death despite tracheotomy. Unusual is the absence of a membranous exudate or mucous plug in the trachea or bronchi. The dyspnea was obviously caused by the severe edema of the subglottic region.

There are a few autopsy records available of patients dying from

so-called laryngotracheobronchitis (Baum,<sup>5</sup> Richards<sup>6</sup>). The autopsy descriptions are meager and are usually confined to the description of the respiratory tract. Lobar pneumonia, pulmonary edema, pneumothorax, atelectasis of the lungs and septicemia are often regarded



FIG. 3

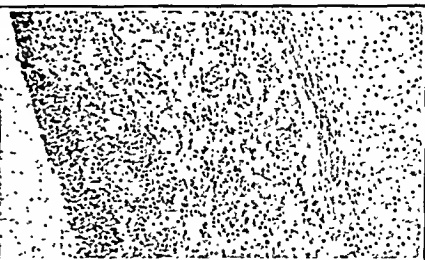


FIG. 4

FIG. 3.—Epiglottis. Note the edema and the relatively few cellular elements. (Iron-hematoxylin-eosin.)  $\times 90$ .

FIG. 4.—Epiglottis. Note the dilatation of the blood-vessels and the inflammatory cells. Iron-hematoxylin-eosin.)  $\times 95$ .

as the cause of death. However, no satisfactory explanation is offered as to a "sudden" and unexpected death (Richards<sup>7</sup>). In the available literature only 1 instance was encountered in which inflammation of the heart is mentioned. DeNavasquez<sup>8</sup> merely stated that "Sections from the heart and lungs revealed severe purulent inflammation and numerous gram negative bacilli." No mention is made of involvement



FIG. 5



FIG. 6

FIG. 5.—Myocardium. Note the inflammatory cells principally in the interstitial tissue. Most of the cells are lymphocytes. (Iron-hematoxylin-eosin.)  $\times 180$ .

FIG. 6.—Myocardium. Note the more or less diffuse infiltration of lymphocytes and a few neutrophils. (Iron-hematoxylin-eosin.)  $\times 150$ .

of the myocardium. It is noteworthy, however, that Jackson and Jackson<sup>9</sup> (Brennemann's "Practice of Pediatrics") stated that pericarditis, myocarditis and endocarditis are frequent and usually fatal complications.

In this series of 5 children, myocarditis was encountered in every instance. It was found because a special effort was made to look for myocarditis: This was done because the children had died unexpectedly and because a similar type of death in other instances, particularly in poliomyelitis, could be explained on the basis of a myocarditis. It must be emphasized, however, that often a number of sections of the myocardium had to be examined histologically before evidence of myocarditis could be demonstrated.

Thus, these 5 patients who died unexpectedly disclosed edema of the epiglottis, the vocal cords and subglottic tissue in the absence of any obstructing pseudomembrane. Acute myocarditis probably was the direct cause of death. It seems likely that in a number of other instances of laryngotracheobronchitis in which children succumbed quickly, death was caused by myocarditis. Baum<sup>5</sup> stated he could not find the cause of death even after autopsy had been performed. It seems obvious that the myocardium was not carefully examined histologically. Also, the high mortality rate in these instances, as stressed by Richards<sup>6</sup> can be explained by the complicating myocarditis. It must be emphasized, however, that because of the absence of an exudate obstructing the air passage, it cannot be definitely stated that the disease of these 5 children actually falls into the classification of acute laryngotracheobronchitis.

As stated before, a clinical diagnosis of myocarditis had not been made, apparently because of the short duration of the disease and the severity of the clinical symptoms which demanded the full attention of the attending physicians. There simply had been no time for the taking of an electrocardiogram. Perhaps a concentrated effort in future cases with the specific purpose of either establishing or ruling out myocarditis will eventually lead to a correct diagnosis. At any rate, it seems, from this investigation that myocarditis in these children was not only present but was the cause of death. For this reason it is obvious that the physician who takes care of such patients must be aware of this complication and be prepared to use supportive measures to forestall if possible death due to myocarditis.

The bacteriologic examination of the throat in these children disclosed the absence of *C. diphtheriæ*. Non-hemolytic streptococci were found in the throat of 3 children. However, there is no evidence that these organisms had actually caused this condition. Orton<sup>2</sup> and his co-workers found various bacteria associated with acute laryngotracheobronchitis. Smith<sup>4</sup> thought that streptococci were the chief offending organisms, although they are usually found in conjunction with other bacteria. Sinclair,<sup>10</sup> MacCready<sup>1</sup> and others are more inclined to ascribe the causative rôle to *Hemophilus influenzae*. As a matter of fact, MacCready remarked that *H. influenzae* Type B causes the most extreme edema in the region of the glottis. However, he also suggested the possibility of a virus infection. Davies<sup>11</sup> found *H. influenzae* in addition to hemolytic streptococci, staphylococci and pneumococci in 12 instances.

Smith<sup>4</sup> described laryngotracheobronchitis in children in an epi-

demic form in Los Angeles during the fall and winter of 1933-34. This series of 5 children was observed over a period of about 5 weeks. These children came from various sections of a large metropolitan area. This alone would speak against the beginning of an epidemic form of this disease. But such a possibility certainly should be borne in mind.

**Summary.** Five children who rapidly developed symptoms of upper respiratory obstruction, and succumbed quickly despite tracheotomy, are recorded. Autopsies disclosed severe laryngeal edema, edema of the epiglottis and subglottic area and acute myocarditis. The edema is interpreted as an early stage of so-called laryngotracheobronchitis. The unexpected death was probably caused by myocarditis. If the attending physician in future instances is aware of this complication, supportive measures might forestall the fatal outcome.

#### REFERENCES

1. MACCREADY, P. B.: Our Changing Conception of Acute Laryngotracheobronchitis, Trans. 49th Ann. Meeting Am. Laryngol., Rhinol. and Otol. Soc., New York, p. 236, 1944.
2. ORTON, H. B., SMITH, E. L., BELL, H. O., and FORD, R. A.: Acute Laryngotracheobronchitis. Analysis of 62 Cases With Report of Autopsies in Eight Cases, Arch. Otolaryngol., 33, 926, 1941.
3. BRENNEMANN, G., CLIFTON, W. M., FRANK, A., and HOLINGER, P. H.: Acute Laryngotracheobronchitis, Am. J. Dis. Child., 55, 667, 1938.
4. SMITH, W. J.: Acute Laryngotracheobronchitis in Children, Arch. Otolaryngol., 23, 420, 1936.
5. BAUM, H. L.: Acute Laryngotracheobronchitis in Children, J. Am. Med. Assn., 91, 1097, 1928.
6. RICHARDS, L.: A Further Study on the Pathology of Acute Laryngotracheobronchitis in Children, Ann. Otol., Rhinol. and Laryngol., 47, 326, 1938.
7. RICHARDS, L.: Acute Laryngotracheobronchitis, Ann. Otol., Rhinol. and Laryngol., 42, 1914, 1933.
8. DENAVASQUEZ, S.: Acute Laryngitis and Septicemia Due to *H. influenzae* (Type B), Brit. Med. J., 2, 187, 1942.
9. JACKSON, CH., and JACKSON, CH. L.: In Practice of Pediatrics by various authors, edited by J. Brennermann, Hagerstown, Md., W. F. Prior, vol. II, chap. 45, p. 6, 1944.
10. SINCLAIR, S. E.: Hemophilus Influenzae, Type B, in Acute Laryngitis With Bacteremia, J. Am. Med. Assn., 117, 170, 1941.
11. DAVIES, J. A. V.: Acute Laryngotracheobronchitis in Children, New England J. Med., 229, 197, 1943.

#### THE LIFE CYCLE OF THE ERYTHROCYTE AFTER SPLENECTOMY AND THE PROBLEMS OF SPLENIC HEMOLYSIS AND TARGET CELL FORMATION

BY KARL SINGER, M.D.\*†

AND

LEO WEISZ, D.V.M.

BOSTON, MASS.

THE question as to whether or not the spleen under physiologic conditions participates actively in erythrocyte destruction is not yet settled. Perusal of the literature reveals such contradictory statements as: the spleen destroys red cells,<sup>37</sup> prepares erythrocytes for

\* Present address: Medical Clinic Boston Dispensary.

† This work was done in the Middlesex University Medical School.

hemolysis elsewhere,<sup>16,37</sup> protects the blood corpuscles from disintegration,<sup>63</sup> or has no influence on the breakdown of erythrocytes at all.<sup>39</sup> Clinical observations demonstrate that excessive hemolysis ceases dramatically after splenectomy in familial spherocytic jaundice and acquired hemolytic anemia, but that removal of the spleen is without curative effect in other hemolytic syndromes. Evaluation of the changes following splenectomy in normal human beings and animals is difficult and equivocal due to the influence of the spleen on qualitative and quantitative bone marrow production and the possible compensatory reaction of other parts of the reticulo-endothelial system.<sup>60</sup>

Recently determination of the longevity of the erythrocyte has been developed into a method for the study of anemia.<sup>8,9</sup> By means of "differential agglutination" (using the agglutinogens M and N to tag the erythrocytes) it has been demonstrated that transfused erythrocytes survive in the circulation for about 80 to 120 days, provided that no other abnormal conditions exist.<sup>9,70</sup> If pathologic red cells are transfused into normal individuals, or if normal red cells are exposed to apparently abnormal hemolyzing activities, valuable information may be obtained.<sup>9</sup> Determination of the survival time of erythrocytes may prove to be particularly significant in testing the hemolyzing systems of the body.

In this paper an attempt is made to attain knowledge on physiologic splenic hemolysis by means of measuring the average life cycle of the erythrocytes before and after splenectomy in dogs. It was thought that the results of these investigations might also provide a basis for clinical studies of splenic function in the various types of hemolytic anemias.

**Material and Methods.** As hematologically normal but splenectomized human beings were not available, determinations of the life cycle of the erythrocyte were performed in dogs. This species was chosen because in dogs splenic functions manifest themselves most distinctly.<sup>30,37,38</sup>

Selection of the method for life cycle determination in animals proved most difficult as serologic procedures are not readily available and the results obtained with other methods are very much at variance. As will be pointed out later only the method of Hawkins and Whipple<sup>27</sup> gives values for the dog comparable to the differential agglutination tests for human beings. Hawkins and Whipple used biliary fistula dogs in which the daily output of bile pigment was first determined over a long period of time. By means of injections of acetylphenylhydrazine or by bleeding a severe anemia was then produced. During the period of regeneration, a new population of young erythrocytes is rapidly launched into the circulation. Following the anemia period the bilirubin output was found to be lowered, as due to the change in the age of the red cell population, less erythrocytes are now destroyed. Observation of the daily bilirubin excretion, then, showed a gradual increase of the bile pigment output which reached a peak after an average of 124 days. This peak was interpreted as being caused by mass disintegration of red cells that, having entered the circulation during the repair period of the anemia, ended their life cycle about the same time. Afterwards the bilirubin output returned gradually to the base line. The hemoglobin level remained fairly constant in the post-anemia period, independent of the bilirubin excretion; as the increased destruction of the erythrocytes at the end of their life cycle occurs gradually and not abruptly, the bone marrow compensates for the augmented daily loss without any difficulty. Hawkins and Whipple<sup>27</sup> performed these determinations in 4 dogs.

Our own experiments were performed in 6 dogs. Only the renal type of biliary fistula<sup>33</sup> was used. In this operation the common bile duct is severed and the gall bladder anastomosed with the right kidney, thus excreting the bile through the urinary passages.

*Care of the Animals.* Before operation the feces were examined for intestinal parasites which are almost always present and may sometimes be the cause of a disturbing anemia. After identification of the parasites proper drugs for their removal were administered. One week after the successful operation, all animals received anti-distemper serum. All dogs were kept in metal metabolism cages. They were fed a constant uniform diet composed of commercial dog food ("Bombo" and "Ken-L-Biskit") and white bread. Water was given *ad libitum*. Furthermore all animals received daily 5 cc. of cod liver oil,  $\frac{1}{2}$  gm. of Fleischmann's yeast (in gelatin capsule), and 1 tablet (5 mg.) of Synkayvite Roche (vitamin K) 3 times weekly. Thus all necessary vitamins were supplied. It may be emphasized that in long-standing experiments with renal biliary fistula dogs the administration of vitamin K is absolutely indicated to prevent a gradual decrease of the prothrombin level which may be the cause of severe hemorrhages. Besides the vitamins, ferrous sulfate (0.2 to 0.4 gm. daily), and sodium taurocholate (0.6 gm. daily, in gelatin capsule) were given.<sup>18,19</sup> This mixture of vitamins, iron and bile salt was administered instead of ox or dog bile, as used by Hawkins and Whipple,<sup>27</sup> in order to avoid any possible absorption and reexcretion of bilirubin.<sup>19</sup>

The weight of the animals was determined weekly and only animals which maintained or gained weight were used. Some of the dogs showed a tendency to diarrhea which was successfully combated by sprinkling the food with bone meal or adding 3 to 5 gm. of  $\text{CaCl}_2$  to the drinking water, or both. The 24 hours urine was collected and chloroform was added as a preservative.

*Bile Pigment Determinations.* (a) *Bilirubin in the urine:* performed daily. Photocolorimetric method of Singer and Kubin.<sup>61</sup>

(b) *Urobilinogen in the feces:* method of Fürth and Singer.<sup>20</sup> After establishment of the fistula determinations of urobilinogen in the feces were performed and only if no trace of urobilinogen was found—proving the presence of a complete bile fistula—were the animals used.

*Hematologic determinations* were performed at least once weekly.

(a) *Hemoglobin:* photoelectric method of Sheard-Sanford.<sup>58</sup> 100% = 15.6 gm./100 cc. of blood. After administration of acetylphenylhydrazine a marked cloudiness in the hemoglobin solution was noticed. This phenomenon is caused by the denaturation of the globin (Morawitz and Pratt<sup>61</sup>) and the cloudiness had to be removed by centrifugation before readings were taken in the colorimeter.

(b) *R.B.C.:* U. S. Bureau of Standards certified Trenner pipets and hemocytometer used; automatic shaker.

(c) *Hematocrit:* venous blood collected in a 5 cc. vial containing dry ammonium oxalate (6 mg.) and potassium oxalate (4 mg.).<sup>29</sup> Centrifugation in Wintrobe type hematocrit tubes for 30 minutes at 3500 r.p.m.

(d) *Reticulocyte count:* wet and dry methods used.

(e) *Coverslip preparations:* stained with Wright's stain for demonstration of target cells and Howell-Jolly bodies.

(f) *Fragility of red cells to hypotonic solutions of NaCl:* the quantitative method of Hunter<sup>32</sup> was used which was slightly modified for adaptation to the Klett Summerson photoelectrocolorimeter, employing micro tubes and 20 c.mm. of blood, added from a Sahli pipet, to 4 cc. of the various hypotonic NaCl dilutions.

(g) *Blood volume determinations:* method of Gibson and Evans<sup>21</sup> using the Evans blue dye and the Klett Summerson photoelectrocolorimeter. Standardization as described by Levinson and MacFate.<sup>40</sup>

(h) *Hemolytic index:* 
$$\frac{\text{bile pigment excretion/day}}{\text{total hemoglobin in grams}} \times 100.$$
<sup>48,60</sup> This index used

in clinical investigations for the interpretation of erythrocyte destruction expresses the bile pigment excretion per day in relation to 100 gm. of hemo-

globin.<sup>48,60</sup> Whereas in clinical studies only bile pigment derivatives (urobilinogen and stercobilinogen) are available, the average daily bilirubin output can be directly measured in the renal biliary fistula dog.

(i) *Prothrombin time*: method of Quick.<sup>57</sup>

(j) *Liver function tests*: bilirubin in the blood, method of Malloy and Evelyn.<sup>44</sup> Cephalin flocculation test, method of Hanger.<sup>40</sup>

*Surgical Procedures.* Operations were performed under nembutal anesthesia. After the establishment of the renal biliary fistula the animals were observed for 6 to 10 weeks until a fairly constant weekly average of bilirubin excretion occurred. Splenectomy, performed 6 to 8 months after the fistula was established, was not tolerated well by these animals. They died 12 to 24 hours after the operation. Postmortem did not show any obvious cause for this unexpected death. The plan to determine the lifetime of the erythrocyte before and after splenectomy in the same animal had to be abandoned. But when splenectomy was performed 4 to 6 weeks after establishment of the renal biliary fistula, no untoward sequelæ were observed. Liver function tests (cephalin flocculation test and bilirubin determination in the serum), performed thereafter, revealed no deviation from the normal. No anemia due to infection with *Bartonella canis* was observed in our splenectomized dogs, an event which otherwise may seriously interfere with this type of experiment (Knutti and Hawkins<sup>36</sup>).

**Results.** *A. Determination of the Average Life Cycle of the Erythrocyte Before Splenectomy.* Red blood cells are thought to be destroyed by fragmentation, phagocytosis and erythrolysis. The latter may possibly be enhanced by the fat content of the food.<sup>18,19,42</sup> As the breakdown of red cells continues after splenectomy, it is evident that participation of the spleen in these mechanisms can only be one feature of the general problem of the means and ways of erythrocyte disintegration. Study of the effect of splenectomy required strictly controlled experimental conditions. As our experimental animals were maintained on a diet different from that used by Hawkins and Whipple,<sup>27</sup> and as, furthermore, a vitamin-bile salt mixture was given instead of whole bile, it was first considered necessary to determine the average life cycle of non-splenectomized dogs under our experimental standard conditions.

As already pointed out, the principle of the method is the production of a severe anemia (by means of acetylphenylhydrazine or bleeding) in a biliary fistula dog which is otherwise completely healthy. The anemia stimulates the entrance of numerous young red cells into the circulation. After regeneration from the anemia there is usually a considerable drop of the bile pigment output below the basic level of the control period. When the newly released erythrocytes are again destroyed, a corresponding increase of the bile pigment is noticeable. Some difficulties were encountered in selecting the starting and the end point of the average lifetime by means of this method. Hawkins and Whipple used the mid-point of the regeneration period as the average starting point. In order to obtain a somewhat sharper defined starting point, we followed the entrance of the new red cells by means of enumeration of the reticulocytes. The reticulocyte peak was then used as the beginning of the estimation of the average life cycle. As the endpoint we selected the day of the highest excretion of bile pigment. As can be seen from Figs. 1 to 6—which were constructed by

plotting the average value of 7 day periods—the right end of the bilirubin excretion curve has a somewhat bell-shaped appearance.

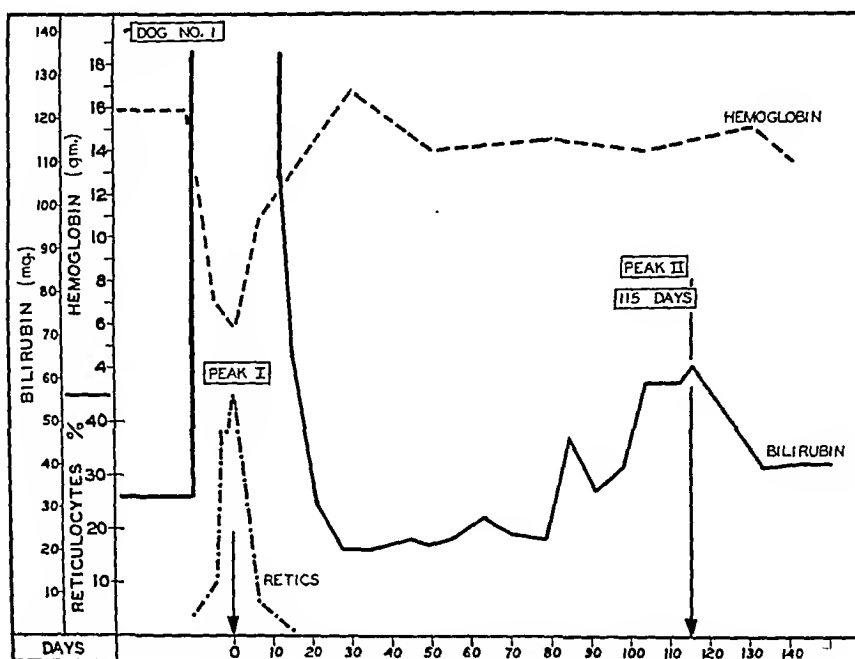


FIG. 1

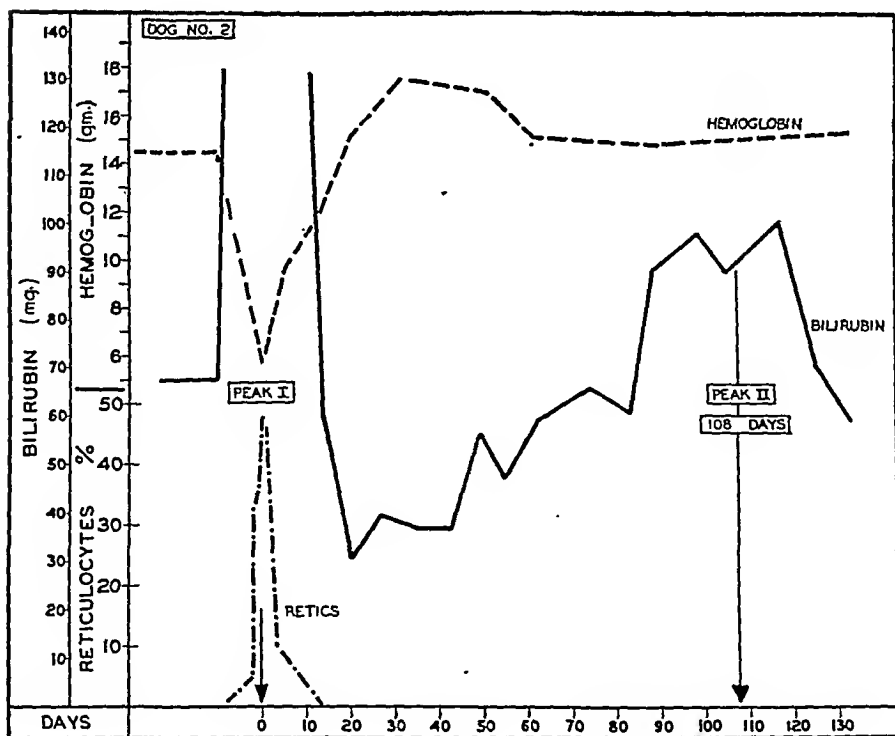


FIG. 2



Such a curve may be expected since the reticulocyte curve which depicts the entrance of new cells into the circulation is also of a similar shape. An absolutely close parallelism between the two curves symbolizing the appearance and disappearance of the investigated red cell population cannot be expected, as too many factors of known and unknown nature are involved in the mechanisms of erythrocyte

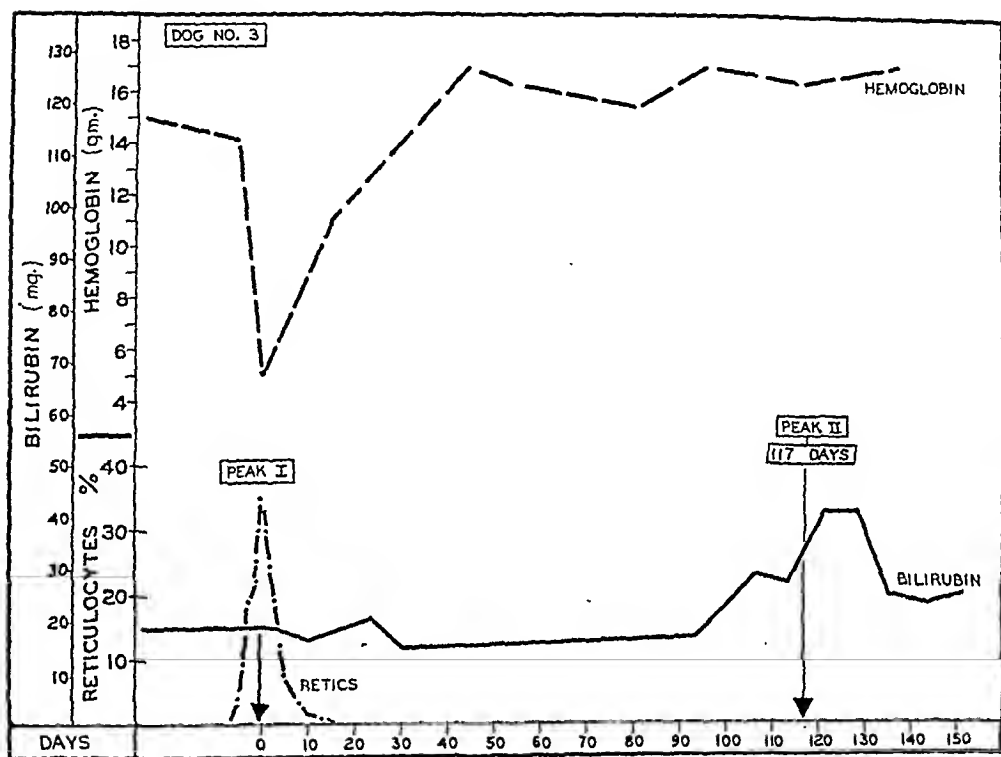


FIG. 3

destruction. The end point of the average lifetime is usually but not always found during the period showing the highest weekly excretion values for bilirubin, *i. e.*, on the "plateau" of the curve. Although the selection of these starting and end points is somewhat arbitrary, the conformity of the results thus obtained is truly remarkable (Table 1).

TABLE 1.—AVERAGE LIFE CYCLE OF THE ERYTHROCYTE BEFORE AND AFTER SPLENECTOMY

Dog No.	Before splenectomy (days)	Dog No.	After splenectomy (days)
1 . . . . .	115	4 . . . . .	110
2 . . . . .	108	5 . . . . .	96
3 . . . . .	117	6 . . . . .	109
Average . . . . .	113	Average . . . . .	105

**Experimental Observations.** Dog 1. Male mongrel, weight fluctuating between 10.1 and 11.2 kg. Average bilirubin excretion during control period before the acetylphenylhydrazine injections 33.3 mg./day. A total of 750 mg.

acetylphenylhydrazine was injected on 4 successive days. This led to an excess output of 2051 mg. bilirubin, corresponding to 59 gm. hemoglobin (1 gm. hemoglobin = 34.9 mg. bilirubin<sup>5,6</sup>). The average hemoglobin content of the blood in the control period was 15.5 gm./100 cc., the total blood volume was 911 cc., giving a total circulating hemoglobin of 141.2 gm. Therefore, at least 41.7% of the total circulating hemoglobin was destroyed. The highest reticulocyte count during the anemia period was 43%, occurring 8 days after the first injection. Complete regeneration of the anemia took place after 23 days. As can be seen from Fig. 1 there was then a considerable drop of the bilirubin output which lasted for about 8 weeks; then a gradual increase took place until it reached a peak of 69.7 mg./day, occurring in the 17th week. The bilirubin excretion then gradually dropped until 2 weeks later it returned to the base level. The average life cycle was thus computed to be 115 days.

Dog 2. Female mongrel, weight gradually increasing from 13.2 to 15.6 kg. Average bilirubin excretion during control period 67.1 mg./day. A total of 1250 mg. acetylphenylhydrazine was injected on 7 successive days; excess output in bilirubin 4246 mg., corresponding to 122 gm. hemoglobin. With an average hemoglobin of 14.5 gm./100 cc. and a total blood volume of 1630 cc., the total circulating hemoglobin was 236.4 gm. Thus 51.7% of the latter were destroyed. The reticulocyte peak was 47%, occurring on the 8th day after the first injection and the anemia was completely regenerated on the 30th day. The then-occurring drop in bilirubin output lasted for about 10 weeks. Then a more abrupt increase took place reaching a peak of 134.7 mg. in the 16th week. After 3 weeks the bilirubin excretion then dropped to the base level. The average life cycle was found to be 108 days.

Dog 3. Female mongrel, weight 6.4 to 7.3 kg. Average bilirubin excretion during control period 19.2 mg./day. The average hemoglobin was 14.5 gm./100 cc., the total blood volume 520 cc., thus the total circulating hemoglobin 75.4 gm. In this animal blood was removed by repeated heart and venipunctures until the hemoglobin dropped to 5.1 gm./100 cc. 300 cc. of blood were thus removed leading to a loss of 43.5 gm. (58%) of the original total hemoglobin. The reticulocyte peak was 35% and the anemia was completely regenerated 25 days after the first bleeding. There was only a slight drop of the bilirubin output for about 13 weeks. Then a gradual increase took place; the highest excretion observed was 59.2 mg. within the 17th week. As can be seen from Fig. 3 this end point of the average lifetime lies on the ascending limb of the bell-shaped curve and a high average excretion of 42 mg. continued for 2 weeks. There was also no complete return to the base level. The average life cycle was computed to be 117 days. We have found that the acetylphenylhydrazine anemia is much better suited for life cycle determination than the anemia produced by bleeding, although almost identical values for the average lifetime were found with both methods.

The average life cycle of our 3 dogs was found to be 113 days (see Table 1) which is in good agreement with the values obtained by Hawkins and Whipple (124 days).

*B. The Life Cycle of the Erythrocytes After Splenectomy.* This was also studied in 3 dogs. As can be seen from Figs. 4 to 6 and Table 1, the average life cycle was not significantly altered by removal of the spleen.

**Experimental Observations.** Dog 4. Female mongrel, weight 12.8 to 14.6 kg. During the control period the average bilirubin excretion was 54.6 mg./day. The hemoglobin fluctuated between 14 and 15.2 gm./100 cc. After splenectomy the bilirubin excretion diminished for several weeks with fluctuations between 38 and 50 mg. with an average of 44.2 mg./day. The hemoglobin dropped to 12.6 gm./100 cc. but after 2 weeks rose to the original level. The circulating blood volume was 1172 cc. before and 1134 cc. 5 weeks after splenectomy. 1600 mg. of acetylphenylhydrazine were injected during

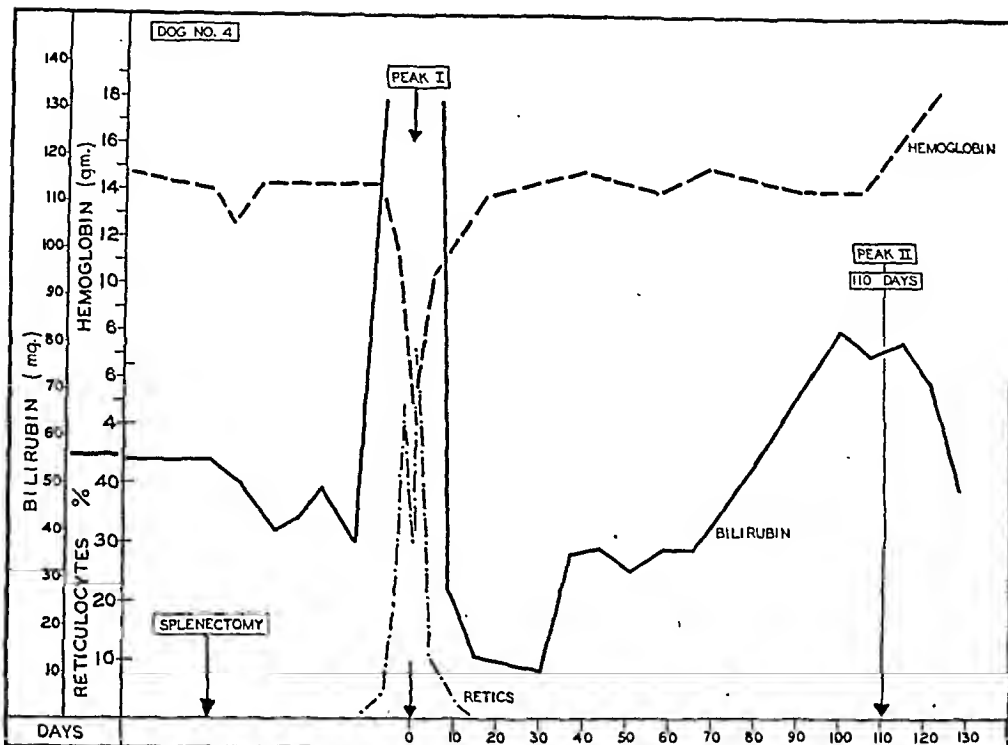


FIG. 4

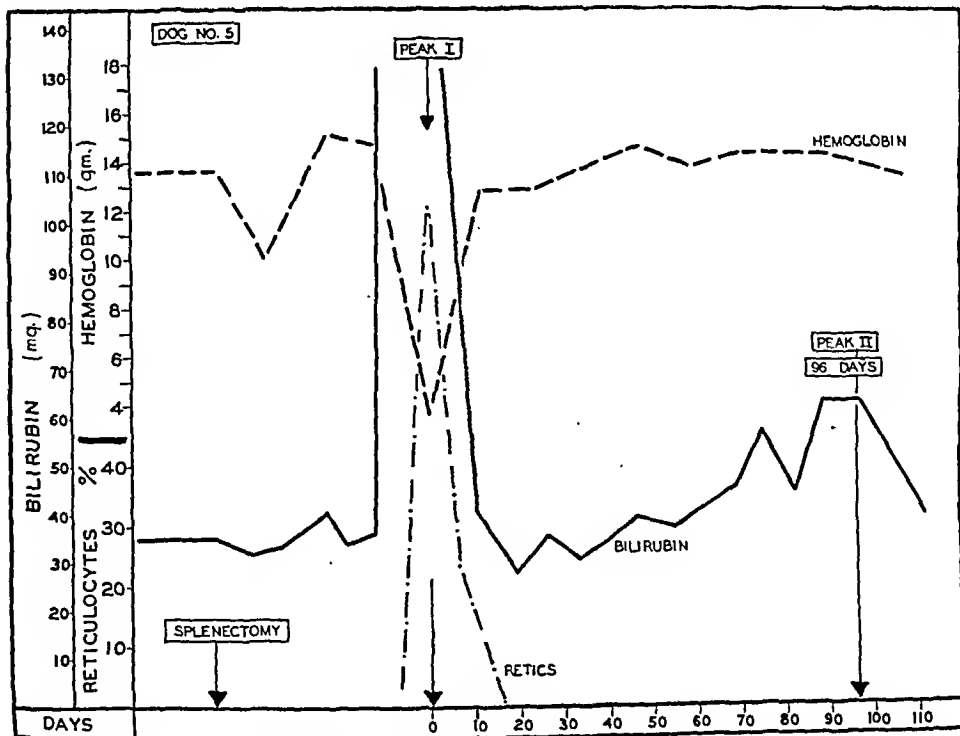


FIG. 5

a period of 9 days. This led to a total excess pigment output of 2689 mg. bilirubin. The hemoglobin dropped to 5.5 gm./100 cc. on the 11th day after beginning of the injections and the anemia was completely regenerated after 29 days. With an average hemoglobin content of 14.2 gm./100 cc. the total circulating hemoglobin was computed to be 161 gm. Therefore, by means of the injections 47.9% of the latter were destroyed. The reticulocyte peak of 62% reticulocytes was observed 11 days after beginning of the injections. After recovery from the anemia the pigment output dropped to a very low level for several weeks, reached the base level after about 80 days, and the highest single pigment output of 119.5 mg. bilirubin was observed on the 110th day within a weekly average of 79 mg. in the 16th week. Then a gradual return to the base level occurred. The average lifetime in this dog was found to be 110 days.

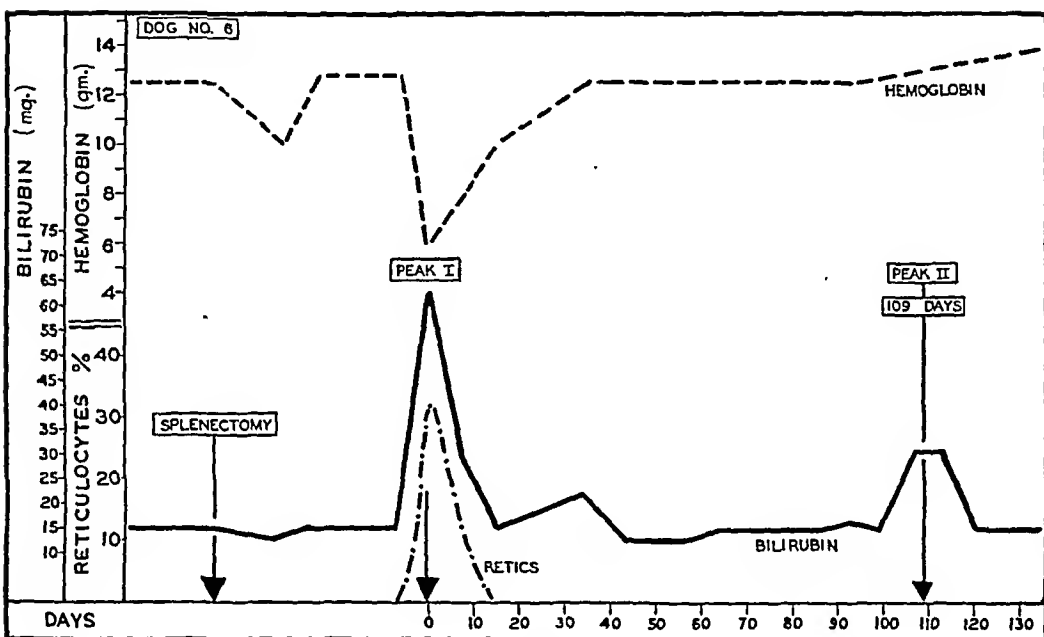


FIG. 6

Dog 5. Female mongrel, weight 9.2 to 12.2 kg. The average bilirubin excretion of the control period was 34 mg./day. The average hemoglobin content was 13.3 gm./100 cc. Following splenectomy the daily bilirubin excretion remained practically unchanged, averaging 35 mg. There was a decrease of the hemoglobin to 9.6 gm./100 cc. 2 weeks after splenectomy, but a few weeks later the hemoglobin regenerated to an average of 14.2 gm./100 cc. The circulating blood volume was 670 cc. Seven weeks after splenectomy 1200 mg. of acetylphenylhydrazine were given during a period of 6 days. This led to a total excess pigment output of 2197 mg. bilirubin. The hemoglobin dropped to 3.4 gm./100 cc. on the 7th day after beginning of the injections. The anemia was completely regenerated after 43 days. With an average hemoglobin content of 14.2 gm./100 cc. the total circulating hemoglobin was computed to be 95.1 gm. Therefore, by means of the injections 66.1% of the circulating hemoglobin were destroyed. The reticulocyte peak was unusually high, namely 83% occurring 10 days after the first injection. Following the regeneration of the anemia the bilirubin output dropped moderately for several weeks; there was then a gradual increase and the highest bilirubin excretion of 94 mg./day was observed on the 96th day following the reticulocyte peak. Then a rapid return to the base level occurred. The

average lifetime in this dog was the shortest observed in our series, namely 96 days.

Dog 6. Female mongrel, weight 5 to 6.8 kg. The average bilirubin excretion of the control period was 15.6 mg./day, the average hemoglobin 12.6 gm./100 cc. As the hemoglobin level did not increase on vitamin B complex, liver and iron and the dog seemed to be perfectly healthy and was gaining weight, it was decided that this animal could be used for the life cycle determination in spite of the relatively low hemoglobin. Following splenectomy the bilirubin excretion remained almost unchanged, averaging 15.4 mg./day. There was a decrease of the hemoglobin to 10 gm./100 cc. 2 weeks after removal of the spleen. Recovery from this temporary anemia followed after 1 week. Due to the relatively low starting hemoglobin level and the small stature of this

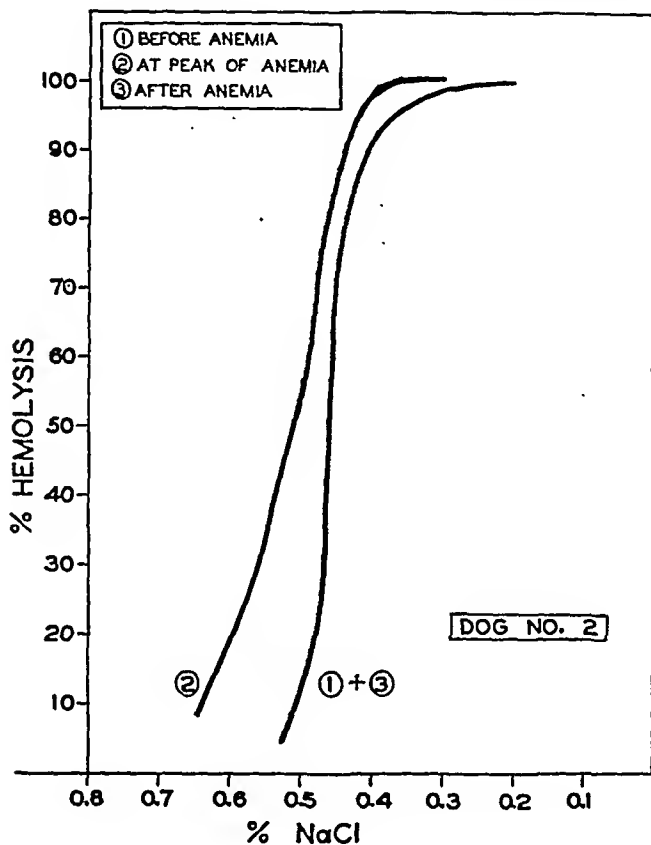


FIG. 7

dog it was decided to produce only a moderately severe anemia. Six weeks after splenectomy 450 mg. acetylphenylhydrazine were given during a period of 4 days. The hemoglobin dropped to 5.9 gm./100 cc. on the 7th day after beginning of the injections. The injections produced an excretion of 425 mg. bilirubin in excess of the daily basic output. With an average hemoglobin content of 12.6 gm./100 cc. and a total blood volume of 425 cc. the total circulating hemoglobin was computed to be 53.6 gm. The excess bilirubin corresponds to 12.2 gm. of hemoglobin. Therefore, by means of the injections at least 22.8% of the circulating hemoglobin were destroyed. The reticulocyte peak was 32%, occurring 7 days after the first injection; complete regeneration of the anemia occurred after 5 weeks. After excretion of the excess pigment the bilirubin output dropped only slightly below the basic level, then showed an unexpected increase with a rapid return to the base level. There was then an abrupt increase starting on the 98th day and the highest daily excretion of 37.3 mg. was noticed on the 109th day. Afterwards the pigment output returned rapidly to the base level.

The average life cycle in the splenectomized animals was 105 days (Table 1) which is 8 days less than in the non-splenectomized dogs. However, such differences lie certainly within the range of physiologic variability.

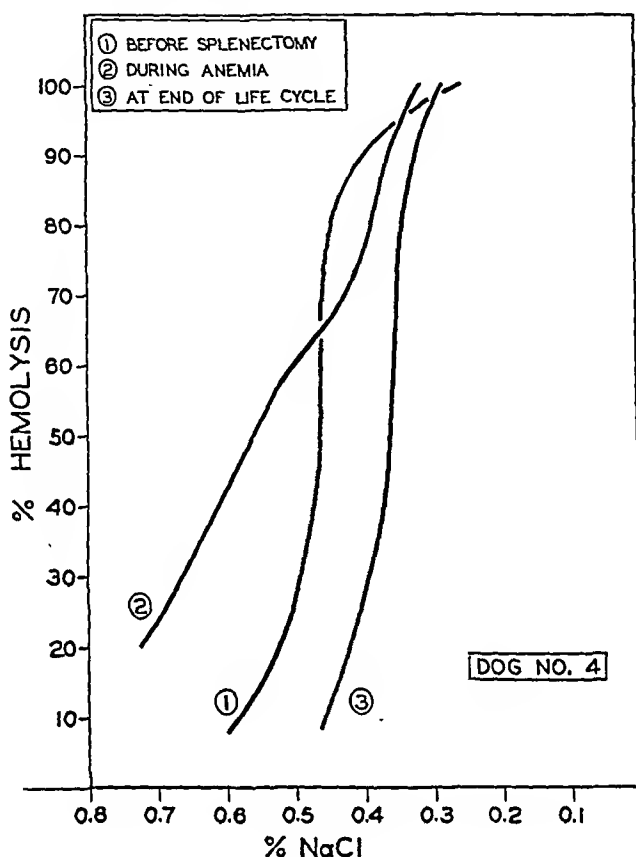


FIG. 8

**Special Observations.** 1. *The Hemoglobin Content and Red Count After Splenectomy.* A temporary mild anemia is known to develop after removal of the normal spleen. Krumbhaar,<sup>38</sup> who has especially studied this phenomenon, states that the red count in his dogs dropped on an average of 1.5 millions with a similar fall of the hemoglobin. The anemia in the dogs reached its average maximum on the 29th day. We, too, observed the development of such a transitory anemia in our dogs in the post-splenectomy state, as can be seen from the figures. In Dog 4 the hemoglobin dropped from 14.2 to 12.6 gm./100 cc. on the 12th day and the red count diminished from 6.4 to 5.5 millions; the hematocrit decreased from 43 to 40. Two weeks later the base levels were reached again. In Dog 5 the post-splenectomy anemia was more pronounced, the hemoglobin decreasing from 13.3 to 9.6 gm./100 cc., the red cell count from 6.2 to 4 millions, and the hematocrit from 36 to 29. Two weeks later the normal levels were reached and afterwards there was a transitory further increase of red cell count and hemoglobin content to 6.4 millions and 15.6 gm./100 cc., respectively. In Dog 6 the hemoglobin decreased from 12.6 to 10 gm./100 cc.,

the red cell count from 5.2 to 4.5 millions, and the hematocrit from 34 to 29 two weeks after operation. Recovery followed rapidly after 1 week. Determination of the life cycle was started in animals only which had completely recovered from the transient post-splenectomy anemia.

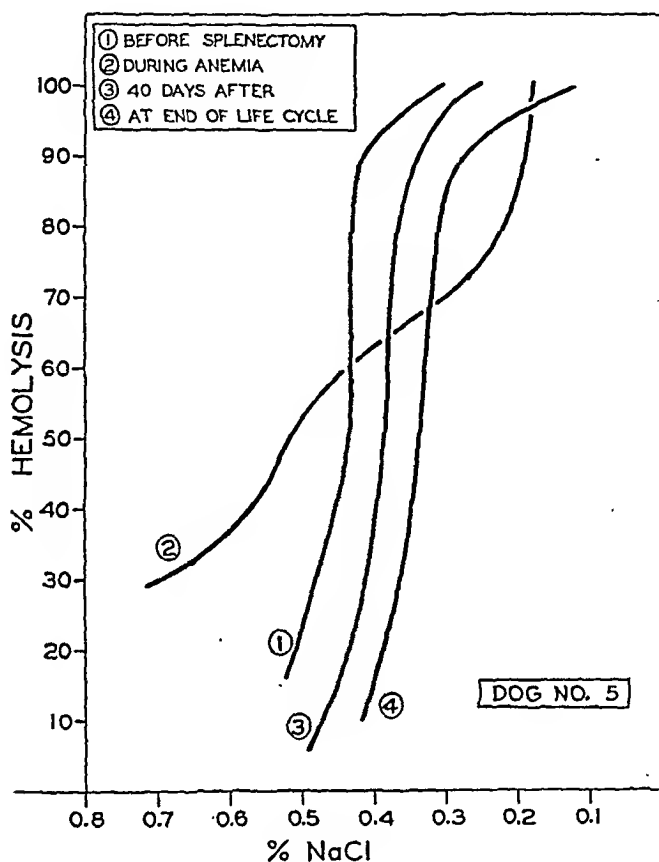


FIG. 9

2. *The Effect of Acetylphenylhydrazine After Splenectomy.* It has been repeatedly reported that hemolytic substances become less effective after splenectomy.<sup>37,38</sup> Cruz and Robscheit-Robbins,<sup>7</sup> using acetylphenylhydrazine, did not observe any difference in this respect. Our own observations show that a larger amount of acetylphenylhydrazine was required in Dog 4 to produce the desired level of anemia than in the control experiments, but that in Dog 5 an unusual severe anemia developed very rapidly. In 2 of our splenectomized animals the reticulocyte output was much higher than in the non-splenectomized dogs. It seems that no definite rules can be established regarding the reaction to acetylphenylhydrazine after splenectomy.

3. *Target Cell Formation and Saline Fragility.* It is a well-known fact that after splenectomy the erythrocytes become more resistant toward hypotonic saline solutions. As has been pointed out in previous papers,<sup>49,60</sup> this is related to an increased thinness of zones of the red cells (leptocytosis) which have in the stained smear the appearance of a "bull's eye" or target. However, no absolute parallelism was

observed between the number of target cells and the decrease in fragility. Like Barrett,<sup>3</sup> and Valentine and Neel,<sup>65</sup> we have noted great variations in the number of target cells in different sections of the smears. This may be due, as Valentine and Neel point out, to difference in the technique of preparing the smears. We have, therefore, abstained from enumerating the target cells, and regard the change in fragility as a better expression of the transformation in the shape of the cells. During the period of the acetylphenylhydrazine anemia, increased fragility and spherocytosis were present. In the non-splenectomized animals the fragility curve returned to normal

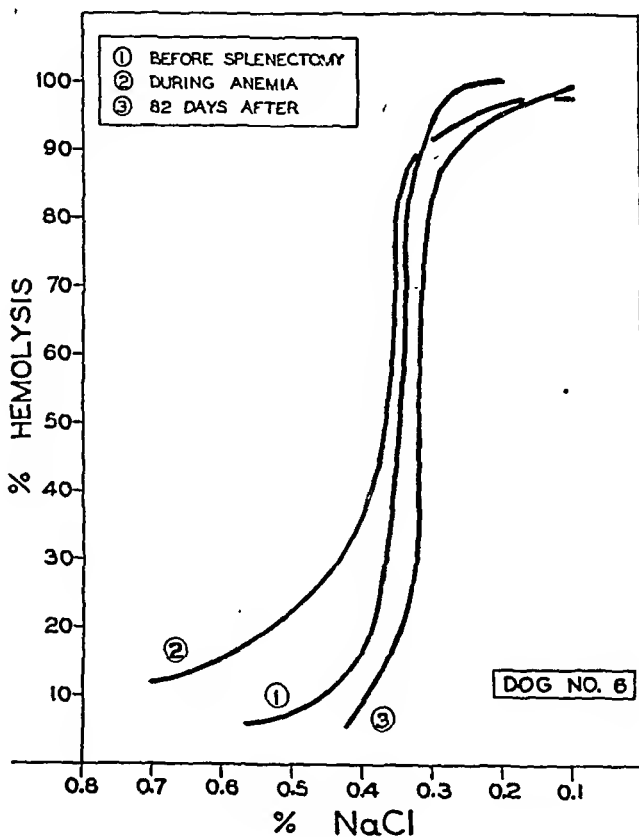


FIG. 10

after about 2 weeks (*e. g.*, Fig. 7). In the splenectomized animals the increase in the resistance to hypotonic saline was very marked (Figs. 8 to 10). As our experiments demonstrate, the average life cycles of the "target cells" (with increased resistance) and of the normal erythrocytes are almost identical. Therefore, the decreased saline fragility does not indicate the existence of any increased *in vivo* resistance of these cells to the forces participating in erythrocyte destruction.

4. *Studies of Pigment Balance (Hemolytic Indices).* Cruz, Hawkins and Whipple<sup>6</sup> have recently stated that the actual bile pigment output in the renal biliary fistula dog corresponds closely to the calculated



amount which can be computed from the known amounts of released hemoglobin after an injection of acetylphenylhydrazine. Their average percentage recovery fluctuated between 67 and 108% with an average of 88%. We have also attempted to compute such a pigment balance based on the figures for the total circulating hemoglobin (*i. e.*,

$\frac{\text{Gm. hgb in 100 cc.} \times \text{blood volume}}{100}$ ), the bilirubin output during the

control period, and the determined average life cycle. As can be seen from the data mentioned above, Dog 1 *f.i.* had during the control period an average bilirubin excretion of 33.3 mg./day. Taking 34.9 mg. bilirubin as corresponding to 1 gm. hemoglobin,<sup>6</sup> this dog excreted the equivalent of 0.95 gm. hemoglobin/day. With an average life cycle of 115 days the calculated amount of destroyed hemoglobin during this period is  $0.95 \times 115 = 109.3$  gm. As the total circulating hemoglobin of the control period was 141.2 gm., the percentage of recovery of bilirubin would amount to 77.4%. Table 2 gives the results of these computations in all our experimental animals.

TABLE 2.—COMPUTATION OF THE PIGMENT BALANCE

Dog No.	Bilirubin output (mg./day)	Computed daily hgb destruction in gm.:	Average life cycle in days	Calc. amt. hgb in gm. destroyed during life cycle period: computed daily hgb destruction (Col. 3) $\times$ life cycle (Col. 4)	Total circulating hgb in gm.:	Percentage of recovery (Col. 6 into Col. 5)
		<u>Av. bilir. excret.</u> 3f.9		<u>Av. hgb/100 cc. <math>\times</math> blood vol.</u> 100		
1	33.3	0.95	115	109.3	141.2	77.4
2	67.1	1.92	108	207.4	236.4	87.7
3	19.2	0.55	117	64.4	75.4	85.4
4	44.2	1.27	110	139.7	161.0	86.8
5	35.0	1.00	96	96.0	95.1	100.9
6	15.4	0.44	109	48.0	53.6	89.6

Average: 88.0  
Range: 77.4–100.9

Our average percentage recovery was 88%, a value identical with that reported by Cruz, Hawkins and Whipple. We believe that the computation of these pigment balances which are based on the determination of the average life-cycle, represents an additional proof for the validity of the method used in our experiments.

The hemolytic index,<sup>60</sup>  $\frac{\text{Bile pigment excretion/day}}{\text{Total circulating hgb}} \times 100$ , was di-

minished after splenectomy only in Dog 4, but remained unchanged in the other 2 experimental animals. This latter finding seems to differ from similar investigations in man<sup>60</sup> where a decrease of the hemolytic index following splenectomy was found in 9 out of 11 cases in which this operation was performed for a previously existing, non-hemolyzing condition. However, a more extensive investigation of this particular problem is required to clarify whether these discrepancies are due to species differences or are due to the fact that in our biliary fistula dogs bilirubin was determined directly, whereas in humans, determination

of bilirubin derivatives (urobilinogen and stercobilinogen) form the basis for calculation of the hemolytic index.

5. *Prothrombin Time.* Diminution of the prothrombin time develops gradually in renal biliary fistula dogs if vitamin K is not administered. Our dogs received 15 mg. of Synkayvite weekly. This dose was amply sufficient to keep the prothrombin at a 100% level.

6. *Histologic Findings.* Postmortem examinations in the 3 splenectomized biliary fistula dogs revealed enlargement of the abdominal lymph nodes. No accessory spleen or hemolymph nodes were found. Histologic examination of lymph nodes and liver did not show any evidence of increased erythrophagocytosis. Studies of the bone marrow, obtained by puncture of the ilium in the living animal did not reveal any pathologic composition; the myeloid-erythroid ratio was within normal limits.

**Discussion.** Our experiments have demonstrated that the average life cycle of the red cells in dogs before and after splenectomy is practically identical, although in the absence of the spleen erythrocytes with increased resistance to hypotonic saline solutions (target cells or leptocytes) are present. Therefore, one must conclude that these "leptocytes" have the same average life cycle as normal red cells. There are several aspects of these findings which are worthy of comment.

*The Validity of Life Cycle Determination.* Determinations of red cell longevity give results which vary widely according to the method used and to the species investigated. In this paper only experiments concerning man and dog will be discussed. In man the most reliable results seem to be obtained by means of the method of differential agglutination. Ashby<sup>1</sup> was the first to transfuse O erythrocytes into recipients of different blood groups and to determine the time required for disappearance of the transfused cells. This technique has become more refined by using the agglutinogens M and N for tagging the transfused erythrocytes. Wiener,<sup>70</sup> Dekkers,<sup>14</sup> Martinet,<sup>46</sup> Mollison and Young<sup>50</sup> and others were thus able to demonstrate that transfused red cells survive for 3 to 4 months in the circulation of normal persons. It is quite obvious that this method does not measure the average life cycle. At the starting point, a mixed population of red cells is transfused; the end point is not sharply defined as the assumption that the youngest cells may survive longest does not take into account the many hazards to which the red cells are exposed during their presence in the circulation. Furthermore, the hemolytic activities may also vary in different persons,<sup>15</sup> depending on dietary habits, exercise and other factors. Thus if, f.i., Rh positive cells are transfused into a Rh negative recipient, it may well be that an anti-Rh factor may start to become active during the course of the determinations, thus leading to wrong results.<sup>9</sup> The findings of the transfusion experiments represent the maximal survival time of "foreign" erythrocytes. As red cells produced on any day may vary to some extent in their quality and thus cope differently with the fluctuating forces active in erythrocyte destruction, the average life cycle may sometimes be appreciably shorter than the maximal survival time.<sup>2</sup> Nevertheless, the estima-

tion of the maximal survival time can be used as a very valuable tool for the study of the pathogenesis of the anemias.

Escobar and Baldwin<sup>17</sup> approached the problem of the estimation of the longevity of the red cells in an entirely different manner. They produced an increase in erythrocyte volume in the circulation by short exposure to low pressure of oxygen and consider the number of days elapsing from the end of the exposure period to the attainment of a normal red cell volume as representing the duration of the life span of the erythrocytes. They found values of 16 to 23 days for dogs and 18 to 30 days for man. Davis<sup>13</sup> produced an experimental polycythemia in dogs by means of exercise, cobalt chloride, and ephedrine. The high erythrocyte counts were reduced by additional administration of choline, mecholyl, or similar agents. He assumes that these depressing drugs act as a "brake" on erythrocyte production until the cell count again reaches the normal level. Based on this assumption, the rate of disappearance of the elevated level of red cells should, in his opinion, establish the rate of natural death of the erythrocytes, and if this process were to continue, calculation of the length of time required for 100% disappearance of the cells should become possible. He found 20 days as the "minimal" length of life of the red cells in dogs. In our opinion, which we share with others,<sup>27,63</sup> the underlying principles and assumptions used in the experiments of Baldwin and Escobar and also of Davis are not physiologic and the results probably of doubtful validity.

The method of Hawkins and Whipple<sup>27</sup> represents the best approach to the problem of longevity of the red cells. Evidence for its validity may be seen in the predictable increase of the bile pigment excretion after regeneration of the anemia, the similarity of the bell-shaped curves illustrating appearance and disappearance of the cells, and also the calculations of the pigment balance from the life cycle, blood volume and bilirubin excretion. Hawkins and Whipple found an average longevity of 124 days in their 4 dogs with a range of 112 to 133 days. Our values are somewhat lower; this may be due to sharper definition of the starting and end points, different feeding and maintenance procedures, or it may only be due to the usual statistical variations.

Study of the life cycle after splenectomy has been rarely undertaken. We found only one paper dealing with this problem. Gordon and Kleinberg<sup>22</sup> examined the longevity of the erythrocytes in guinea pigs before and after splenectomy, using the method of Escobar and Baldwin. Before splenectomy the values obtained were 22 to 28 days, after splenectomy 32 to 38 days. Stephens<sup>63</sup> has criticized these experiments. The discrepancy between our findings and those of Gordon and Kleinberg can be explained as due to difference of the methods employed and possibly also to species differences. Unfortunately, no pertinent investigations in splenectomized human beings in the absence of any hematologic disorders have so far been performed.

*The Significance of the Life Cycle Determination After Splenectomy to the Problem of Physiologic Erythrocyte Destruction.* Demonstration of the almost identical average life cycle before and after splenectomy

seems to indicate that "active" participation of the spleen in the physiologic breakdown processes of the erythrocytes is (1) negligible or absent, or (2) can be entirely compensated by extrasplenic activities. This is contrary to the still widespread belief that the spleen is the most important organ involved in the disintegration of red cells. The reason for this belief is easily understood, if one is familiar with the splendid therapeutic effect of splenectomy in certain hemolytic anemias. Lauda,<sup>39</sup> in his excellent monograph on the physiology of the spleen in 1933, has critically reviewed all the evidence in support of splenic hemolysis. According to this author, it is necessary to differentiate between passive and active hemolysis of the spleen. There is no doubt that this organ takes part in removing the débris of red cells which have already disintegrated in the circulation (scavenger function). The spleen functions as the lymph node of the blood. The concept, however, that the spleen actively removes and destroys red cells under normal conditions does not withstand rigorous criticism in Lauda's opinion.

Erythrophagocytosis has been observed in the spleen but there is now general agreement that this mechanism plays, if any at all, only a very insignificant rôle.<sup>34,39,43</sup> Knisely<sup>35</sup> was unable to notice any erythrophagocytosis in the transilluminated living spleen, but observed it in the dying animal or after traumatization.

Development of compensatory hemolymph nodes after extirpation of the spleen has also been occasionally observed. However, Meyer<sup>47</sup> found no hemolymph nodes in 8 splenectomized dogs and Warthin<sup>66</sup> discovered some in only 2 of his 24 animals. Pearce, Krumbhaar and Frazier<sup>53</sup> found an increase of the endothelial cells of the sinuses of various lymph nodes, but no evidence of pigment phagocytosis. Increased phagocytic activity in the liver after splenectomy is difficult to assess.<sup>54</sup> In dogs, Pearce, Krumbhaar and Frazier<sup>53</sup> found no proliferation of the Kupffer cells and no evidence of increased phagocytosis after splenectomy.

Changes in the bilirubin metabolism following splenectomy are often considered as significant indirect evidence of an active hemolytic function of the normal spleen. Mann<sup>45</sup> and others have demonstrated that the blood of the splenic vein contains more bilirubin than the blood of the splenic artery, but this increase is exceedingly small and only discernible by spectroscopic methods. Lauda interprets it as a manifestation of "passive hemolysis." Recently Watson and Paine<sup>67</sup> explain this increase as possibly caused by the intracorpuseular degradation of hemoglobin to bilirubin during erythrosthesis in the spleen. In 1941 one of us, together with Miller and Dameshek,<sup>60</sup> described a decrease of the urobilinogen excretion and the hemolytic index in 11 splenectomized individuals in whom the spleen had been removed for causes other than previously existing hemolytic anemia. This decrease of the hemolytic index was attributed to the absence of the splenic component in the hemolytic activities. In our present dog experiments, however, no constant diminution of the hemolytic index was demonstrable. At the present time these contradictory findings

cannot be fully explained. They may be due to species differences. On the other hand, the lowered hemolytic index may require another explanation, as the intricacies of bile-pigment metabolism are not yet fully understood.<sup>68</sup> As will be discussed below, there is now other evidence available which makes it more likely that active splenic hemolysis under physiologic conditions in man is also absent or insignificant. This whole problem requires further correlated studies, particularly determination of the survival time of the red cells in normal splenectomized human beings.

*The Effect of Splenectomy in Hemolytic Anemias.* Splenectomy has a curative effect in spherocytic familial jaundice and often in acquired hemolytic anemia,<sup>11,63</sup> but only a transient one or no effect at all in the other types of hemolytic disorders. Interpretation of the results of splenectomy are still unsatisfactory, because of scarcity of our knowledge of normal splenic function and of the mechanisms involved in the various types of hemolytic anemias. In the following, the hypothesis is advanced that splenic hemolysis is conditioned by the presence of pathologic red cells which circulate through the organ, but that normal erythrocytes are not attacked.

In familial hemolytic jaundice spherocytosis continues to exist after splenectomy. The increased fragility of the red cells may stay unaltered or may become slightly diminished but still remains within pathologic range.<sup>8,63</sup> In spite of the continuous presence of abnormal cells, hemolysis ceases abruptly after removal of the spleen and pigment metabolism becomes entirely normal.<sup>60</sup> The most astonishing feature in this return to normal—often not sufficiently appreciated—is the fact that the extrasplenic hemolyzing activities of the body treat these abnormal erythrocytes in a normal manner. Continuation of hemolysis after splenectomy is extremely rare and always accompanied by other atypical features.<sup>23</sup> The spherocytes in familial hemolytic jaundice are, therefore, able to fulfill their function as hemoglobin carriers properly only in the absence of the spleen. Increased function of the spleen—hemolytic hypersplenism—was supposed to explain this phenomenon.<sup>16,39</sup> Recently several experiments have been performed which show that this interpretation is not tenable. Lloyd<sup>41</sup> in 1941 demonstrated that spherocytes obtained from splenectomized cases of familial spherocytic jaundice were rapidly destroyed when transfused into a normal recipient, that is, upon coming into contact with a normal organ. Dacie and Mollison<sup>9</sup> transfused normal cells into patients with familial hemolytic anemia and found a normal survival time of 100 to 130 days. On the other hand, the survival time of spherocytes which were transfused into normal individuals was not more than 14 days. Normal red cells, when given simultaneously with spherocytes to the same normal recipient, had a normal survival time, whereas the spherocytes were rapidly destroyed. These experiments show conclusively that the normal spleen destroys the abnormal cells selectively and that the supposedly pathologic spleen does not attack the normal cells in an abnormal way. No hemolytic hypersplenism is, therefore, demonstrable in familial hemolytic jaundice.

That not only spherocytes but also other abnormal cells as well are affected by splenic hemolysis may be seen from an analysis of the effect of splenectomy in pernicious anemia. Before the discovery of liver treatment splenectomy was recommended in this disorder. It had no curative effect but was often followed by a transient improvement of the anemia. Eppinger<sup>16</sup> investigated the bile pigment metabolism before and after splenectomy in his cases of pernicious anemia and found a marked diminution of the urobilinogen output after removal of the spleen. As the qualitative production of the bone marrow was apparently not altered and abnormal erythrocytes (megalocytes) continued to enter the circulation, this can only be explained on the basis of a diminution of erythrocyte destruction caused by the removal of the spleen. Morawitz<sup>52</sup> in 1928 demonstrated that the erythrocytes in pernicious anemia have a much shorter life span than normal cells. He transfused normal red cells into a non-splenectomized case of pernicious anemia to such an extent that the majority of the red cells present in the patient's circulation belonged to the donor's group. As the anemia improved for a longer period of time but no change in the pigment output became noticeable, it is evident that the transfused normal erythrocytes survived much longer than the pathologic megalocytes. In the light of the findings of Eppinger and Morawitz it is apparent that the spleen also destroys megalocytes selectively in pernicious anemia. If a return to qualitatively normal bone marrow production is induced by liver treatment the abnormal cells disappear from the circulation and, therefore, abnormal hemolyzing activities are not noticeable any longer.

Participation of the spleen in the disintegration of erythrocytes is apparently conditioned by abnormal properties of the red cells, which come into contact with this organ.

In acquired hemolytic anemia the red cells may or may not be spherocytic and may or may not be more fragile to hypotonic saline than normal ones.<sup>11</sup> Splenectomy often cures the disease. If spherocytes are present they disappear permanently after removal of the spleen—in contradistinction to familial hemolytic jaundice.<sup>28,60</sup> From the standpoint of our hypothesis the cells must first be rendered spherocytic in order to become eligible for destruction by the spleen.

By what finer mechanism the spleen selects the pathologic red cells for disintegration is not definitely known. Ham and Castle<sup>26</sup> believe that intravascular stasis is the immediate mechanism, resulting in increased blood destruction in hemolytic anemias characterized by increased fragility of the red cells. They demonstrated that the saline fragility of the erythrocytes in the normal spleen increased in their experimental animals when prolonged stasis was induced by nembutal anesthesia. As Dacie<sup>8</sup> points out, this hypothesis is difficult to reconcile with the observation that normal erythrocytes are apparently not attacked by the greatly engorged spleen in spherocytic jaundice, whereas the spherocytes are rapidly destroyed. Furthermore, increased blood destruction should be demonstrable in all disorders with enlargement and engorgement of the spleen, which, however, is not

borne out by clinical experience. Whipple<sup>69</sup> believes that normal discoidal cells have no difficulties in traversing the spleen whereas spherocytes, being thicker cells, are unable to pass through the stomata of the splenic sinuses. As splenic hemolysis is not only demonstrable in the presence of spherocytes but other pathologic cells as well, this explanation is also not completely satisfactory. The question whether tissue and, or, blood lysins (lysolecithin) are of any real significance has also not yet been fully elucidated.<sup>55,59</sup>

But whatever the mechanism, splenic hemolysis seems to be selective, conditioned by the presence of pathologic properties of the red cells passing through the organ. Normally any hemolytic "activity" of the spleen, as can be seen from the studies of determination of the life cycle and survival time, appears to be absent or negligible. Hemolytic anemias are, therefore, not caused by a "primary" increase of an existing physiologic function of the spleen. The concept of a "hemolytic hypersplenism" does not seem to be tenable.

*The Relationship of the Spleen to Target Cell Formation.* The relations which undoubtedly exist between the shape of the red cell, its hypotonic saline fragility and splenic function are difficult to interpret. The following facts may be considered as established: (1) Spherocytic cells, being thicker and, therefore, more fragile,<sup>24</sup> are liable to disintegration by or in the spleen.<sup>11</sup> (2) Red cells leaving the spleen seem to be more fragile than those entering the organ.<sup>26,27,37</sup> This swelling of the erythrocytes may be caused by erythrostasis.<sup>26</sup> (3) Splenectomy leads to the presence of red cells in the circulation which are thinner than normal (leptocytes, target cells) and show increased saline resistance.<sup>3,38,49,60</sup>

If the saline fragility of the erythrocytes were an indicator of their vulnerability to the forces of blood destruction in general, it could not be explained why the spherocytes in familial hemolytic jaundice are not as rapidly destroyed after splenectomy.<sup>8</sup> Furthermore, *in vitro* abnormally resistant cells should also be more resistant *in vivo*. This is not the case as our life cycle experiments after splenectomy demonstrate. One may assume then that the saline fragility test indicates only the vulnerability of the red cells to splenic destruction. This would correlate the effect of splenectomy in acquired and in familial spherocytic anemia. The function of the normal spleen in rendering the red cells more fragile would, however, be insignificant or negligible, as lack of this function obviously does not prolong the longevity of the cells. Non-spherocytic cells may also be affected by the spleen and leptocytes which are more resistant to saline may rapidly hemolyze *in vivo*, *i.e.*, in Cooley's anemia. There is, therefore, no true parallelism between the changes in saline fragility and the tendency of the erythrocytes to rapid disintegration. Alteration in the shape of the red cells as indicated by the fragility tests is probably caused or accompanied by "structural" defects which may be of much greater biologic significance.

Two possible mechanisms may be operating in the development of leptocytosis after splenectomy.<sup>8,60</sup> First, the absence of the normal

spleen which when present increases slightly the fragility of the erythrocytes circulating through it. Secondly, the production of thinner cells by the bone marrow after removal of the controlling influence of the spleen. That bone marrow production is under splenic control can be seen from the almost regular appearance of Howell-Jolly bodies in several species after splenectomy.<sup>31,38,53,60</sup> We are more inclined to believe in the importance of the second mechanism. Clinically, target cells are seen not only after splenectomy but also after hemorrhage,<sup>4</sup> in sickle cell anemia,<sup>25</sup> in Mediterranean anemia and related syndromes,<sup>10,12,62,64,65,71</sup> in long-standing liver diseases (cirrhosis, metastases),<sup>3,60</sup> and in steatorrhea.<sup>3</sup>

Of particular interest is the occurrence of leptocytes in the various syndromes related to Mediterranean anemia<sup>12,62,65,71</sup> (target oval cell syndromes of Dameshek,<sup>12</sup> thalassemia minor of Valentine and Neel<sup>65</sup>). Recent studies of the members of families in which Cooley's anemia occurred have demonstrated that clinical pictures exist in which target cells, oval and stippled cells are present, with a hypochromic anemia, refractory to iron medication, but without the signs of increased hemolysis. Transitions may be found to the fully developed, severely hemolytic Cooley's anemia.<sup>12,65</sup> According to our investigations, leptocytes with increased saline resistance occurring in the post-splenectomy state have a normal life duration. In these Mediterranean syndromes the leptocytes, however, have a variable tendency to rapid disintegration. Another factor is, therefore, involved, not directly related to the shape and fragility of the cells. In the Mediterranean syndromes a disturbance in hemoglobin formation and also a faulty structure of the erythrocytes appear to exist. We believe that the degree of the structural defect is responsible for the tendency of these erythrocytes to undergo rapid destruction. The alterations in shape and fragility, however, are in themselves no indication of the life expectancy of these red cells.

We are fully aware of the hypothetical nature of some of the statements made in this discussion which will probably arouse dissent from other investigators. But we feel certain of general agreement that determinations of the average life cycle or the survival time should be more frequently employed for elucidation of controversial hematologic problems. These methods promise to become a very valuable tool in clinical investigations.

**Summary and Conclusions.** 1. The average life duration of the red cell before and after splenectomy in dogs was found to be practically identical, namely 113 days and 105 days respectively. After splenectomy the red cell population contained numerous target cells (leptocytes) with increased resistance to hypotonic saline solutions. Therefore, it must be concluded, that the longevity of these abnormal cells is not prolonged.

2. Participation of the spleen in physiologic blood destruction seems to be absent or negligible. In certain hemolytic anemias (spherocytic familial jaundice, acute hemolytic anemia, pernicious anemia) splenic hemolysis is present; it is selective, conditioned by abnormal properties



of the erythrocytes which circulate through the organ. No clear evidence is available for the existence of a primary hemolytic "hyper-splenism."

3. In the various Mediterranean syndromes, target cells with increased saline resistance are demonstrable, but, differing from the post-splenectomy state, show a variable tendency to undergo rapid disintegration. It is believed that this tendency is related to a structural defect of these erythrocytes, occurring independently from the changes in shape and fragility.

The authors are indebted to Hoffmann-La Roche, Inc., for the supply of Synkavite used in this work.

#### REFERENCES

1. ASHBY, W.: *J. Exp. Med.*, **34**, 127, 1921.
2. BAAR, H. S., and LLOYD, T. W.: *Arch. Dis. Child.*, **18**, 124, 1943.
3. BARRETT, A. M.: *J. Path. and Bact.*, **46**, 603, 1938.
4. BOHRD, M. G.: *AM. J. MED. SCI.*, **202**, 869, 1941.
5. CRUZ, W. O.: *AM. J. MED. SCI.*, **202**, 781, 1941.
6. CRUZ, W. O., HAWKINS, W. B., and WHIPPLE, G. H.: *AM. J. MED. SCI.*, **203**, 848, 1942.
7. CRUZ, W. O., and ROBSCHT-ROBBINS, F. S.: *AM. J. MED. SCI.*, **203**, 28, 1942.
8. DACIE, J. V.: *Quart. J. Med.*, **46**, 101, 1943.
9. DACIE, J. V., and MOLLISON, P. L.: *Lancet*, **1**, 550, 1943.
10. DAMESHEK, W.: *AM. J. MED. SCI.*, **200**, 445, 1940.
11. DAMESHEK, W., and SCHWARTZ, S. O.: *Medicine*, **19**, 231, 1940.
12. DAMESHEK, W.: *AM. J. MED. SCI.*, **205**, 643, 1943.
13. DAVIS, J. E.: *J. Lab. and Clin. Med.*, **20**, 848, 1943.
14. DEKKERS, H. J. W.: *Acta med. Scand.*, **99**, 587, 1939.
15. DENSTEDT, O. F., OSBORNE, D. E., STANSFIELD, H., and ROCKLIN, I.: *Canad. Med. Assn. J.*, **48**, 477, 1943.
16. EPPINGER, H.: *Die hepatolienalen Erkrankungen*, Berlin, Springer, 1920.
17. ESCOBAR, R. A., and BALDWIN, F. M.: *Am. J. Physiol.*, **107**, 249, 1934.
18. FREEMAN, L. W., and JOHNSON, V.: *Am. J. Physiol.*, **130**, 723, 1940.
19. FREEMAN, L. W., LOEWY, A., MARCHELLO, A., and JOHNSON, V.: *Proc. Fed. Am. Soc. Exp. Biol.*, **1**, 25, 1942.
20. FÜRTH, O., and SINGER, K.: *Ztschr. f. exp. Med.*, **69**, 152, 1929.
21. GIBSON, J. G., 2d, and EVANS, W. A.: *J. Clin. Invest.*, **16**, 301, 1937.
22. GORDON, A. S., and KLEINBERG, W.: *Proc. Soc. Exp. Biol. and Med.*, **38**, 360, 1938.
23. GRIPWALL, E.: *Acta med. Scand.*, Suppl. 36, 1938.
24. HADEN, R. L.: *AM. J. MED. SCI.*, **183**, 441, 1934.
25. HADEN, R. L., and EVANS, F. D.: *Arch. Int. Med.*, **60**, 133, 1937.
26. HAM, T. H., and CASTLE, W. B.: *Proc. Am. Phil. Soc.*, **82**, 411, 1938.
27. HAWKINS, W. B., and WHIPPLE, G. H.: *Am. J. Physiol.*, **122**, 418, 1939.
28. HEILMEYER, L.: *Deutsch. Arch. f. klin. Med.*, **178**, 89, 1935.
29. HELLER, V. G., and PAUL, H.: *J. Lab. and Clin. Med.*, **19**, 777, 1934.
30. v. HERRATH, E.: *Med. Klin.*, **34**, 1355, 1938.
31. HIRSCHFELD, H., and WEINERT, H.: *Berl. klin. Wehnschr.*, **22**, 1026, 1914.
32. HUNTER, F. C.: *J. Clin. Invest.*, **19**, 691, 1940.
33. KAPSINOW, R., ENGLE, L. P., and HARVEY, S. C.: *Surg., Gynec. and Obst.*, **39**, 62, 1924.
34. KLEMPERER, P.: *The Spleen*, Downey's Handbook of Hematology, New York, Hoeber, 1938.
35. KNISELY, M. H.: *Anat. Rec.*, **65**, 23, 131, 1936.
36. KNUFT, R. E., and HAWKINS, W. B.: *J. Exp. Med.*, **61**, 115, 1935.
37. KRUMBHAAR, E. B.: *Phys. Rev.*, **6**, 160, 1926.
38. KRUMBHAAR, E. B.: *AM. J. MED. SCI.*, **184**, 215, 1932.
39. LAUDA, E.: *Die normale und pathologische Physiologie der Milz*, Berlin, Urban & Schwarzenberg, 1933.
40. LEVINSON, S. H., and MACFATE, R. A.: *Clinical Laboratory Diagnosis*, Philadelphia, Lea & Febiger, 1943.
41. LLOYD, T. W.: *On the Etiology of Acholuric Family Jaundice*, Oxford University Thesis, 1941.

42. LOEWY, A., FREEMAN, L. W., MARCHELLO, A., and JOHNSON, V.: *Am. J. Physiol.*, 138, 230, 1943.
43. LUBARSCH, O.: *Die Milz, Henke-Lubarsch Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Vol. I, 1927.
44. MALLOY, H. T., and EVELYN, K. H.: *J. Biol. Chem.*, 122, 597, 1937.
45. MANN, F.: *Am. J. Physiol.*, 76, 306, 1926.
46. MARTINET, R.: *Le Sang*, 12, 15, 1938.
47. MEYER, A. W.: *J. Exp. Zool.*, 16, 241, 1914.
48. MILLER, E. B., SINGER, K., and DAMESHEK, W.: *Arch. Int. Med.*, 70, 722, 1942.
49. MILLER, E. B., SINGER, K., and DAMESHEK, W.: *Proc. Soc. Exp. Biol. and Med.*, 49, 42, 1942.
50. MOLLISON, P. L., and YOUNG, M.: *Quart. J. Exp. Physiol.*, 30, 313, 1940.
51. MORAWITZ, P., and PRATT, J. H.: *München. med. Wchnschr.*, 55, 1817, 1908.
52. MORAWITZ, P.: *Deutsch. Arch. f. klin. Med.*, 159, 85, 1928.
53. PEARCE, R. M., KRUMBHAAR, E. B., and FRAZIER, O. H.: *Spleen and Anemia*, Philadelphia, Lippincott, 1918.
54. PERLA, D., and MARMORSTON, J.: *The Spleen and Resistance*, Baltimore, Williams & Wilkins, 1935.
55. PONDER, E.: *J. Gen. Physiol.*, 27, 483, 1944.
56. QUEEN, F. B., HAWKINS, W. B., and WHIPPLE, J. H.: *J. Exp. Med.*, 57, 399, 1933.
57. QUICK, A. J.: *The Hemorrhagic Diseases*, Springfield, Ill., Thomas, 1942.
58. SHEARD, C., and SANFORD, A. M.: *J. Lab. and Clin. Med.*, 14, 550, 1929.
59. SINGER, K.: *J. Clin. Invest.*, 20, 153, 1941.
60. SINGER, K., MILLER, E. B., and DAMESHEK, W.: *AM. J. MED. SCI.*, 202, 171, 1941.
61. SINGER, K., and KUBIN, R.: *J. Lab. and Clin. Med.*, 28, 1042, 1943.
62. SMITH, C.: *Am. J. Dis. Child.*, 65, 681, 1943.
63. STEPHENS, J. G.: *J. Physiol.*, 95, 92, 1939.
64. STRAUSS, B. M., DALAND, G. A., and FOX, H. J.: *AM. J. MED. SCI.*, 201, 30, 1941.
65. VALENTINE, W. N., and NEEL, J. V.: *Arch. Int. Med.*, 74, 185, 1944.
66. WARTHIN, A. S.: *Proc. Soc. Exp. Biol. and Med.*, 14, 39, 1916.
67. WATSON, C. J., and PAINE, J. R.: *Trans. Assn. Am. Phys.*, 57, 249, 1942.
68. WATSON, C. J.: *New England J. Med.*, 227, 665, 705, 1942.
69. WHIPPLE, A. O.: *Trans. Coll. Phys. Phila.*, 8, 203, 1941.
70. WIENER, A. S.: *Bloodgroups and Transfusion*, Springfield, Ill., Thomas, 1943.
71. WINTROBE, M. M., MATTHEWS, E., POLLACK, R., and DOBRYNS, G. M.: *J. Am. Med. Assn.*, 114, 1530, 1941.

## GENERAL ACQUIRED ANHYDROSIS

BY HUGO T. ENGELHARDT, M.D.\*

INSTRUCTOR OF MEDICINE

AND

J. P. MELVIN, JR., M.D.

ASSISTANT IN MEDICINE

NEW ORLEANS, LA.

(From the Department of Medicine, Tulane University, School of Medicine and Charity Hospital of Louisiana)

THERE are many reports in the medical literature of individuals who do not possess the ability to sweat. By far the majority belong to the group exhibiting hereditary ectodermal dysplasia.<sup>1,2,5-7,9-14,16,17</sup> Although this form of dysplasia is by no means common, acquired anhydrosis is even more of a rarity. Exhaustive search of available literature reveals only one such instance, that of Fog,<sup>8</sup> of a previously well individual who lost the ability to sweat. His patient was a 27 year old white male who possessed normal sweat secretions until he suffered a long febrile illness (paratyphoid fever). This occurred 6 years prior to Fog's observations. Three months following this ill-

\* Present address is Humble Building, Houston, Texas.

ness, the patient noticed that he could not perspire and suffered from a sensation of precordial oppression and facial congestion. In addition, he felt as though his entire body was overheated. These attacks would manifest themselves, not while working, but after he had stopped and was resting in a cool place. He noticed mild febrile states resulting in temperature increases to 102° F. Scaly skin was also noticed and treated with cold cream. Other secretions, such as from lacrimal and salivary glands, showed no abnormalities. Physical examination revealed no evidence of any organic, nervous or metabolic disease. By the use of artificial fever, pilocarpine injection and muscular activity the patient's inability to sweat was demonstrated. Histologic examination revealed that about one-half of the sweat glands had the structural characteristics of normal apocrine glands. The remainder appeared to be abnormal and presented cystic hollows covered with absolutely flat cells with only the nuclei clearly visible. The eccrine glands revealed no abnormalities. Fog concluded that the pathologic condition was localized in the heat center or centers of the hypothalamus.

Of interest also is the observation of Beckman and Horton<sup>2</sup> on a 36 year old white female who gave a history of heat intolerance since the 11th year of her life. From that time until the age of 26, it became necessary for her to live in the cooler basement of her home during the summer months. She stated that she had been dyspneic and unable to walk whenever the environmental temperature exceeded 85° F. At times this was so severe as to necessitate bed rest for as long as 1 month. She stated that even in hot weather she had never been able to perspire. She appeared to be above average in intelligence and a stable type of individual. Physical examination revealed good bodily health. In order to test her ability to sweat, the entire surface of the patient's skin was striped with a saturated alcoholic solution of cobaltous chloride and she was then placed in an aluminum baker. The temperature was maintained for 1 hour at 140° F. This experiment resulted in only slight sweating in the axillæ, the elbows, over the sternum, the soles of the feet and palms of the hands. She was given  $\frac{1}{5}$  gr. of pilocarpine (0.013 gm.) subcutaneously. This resulted in generalized sweating over the entire body. Because of the fact that she was examined in cool weather, these observers suggested that she return during the coming summer. She did so and was observed in one of her attacks in which she was unable to walk at a normal rate. It was felt after neurologic consultation, that the disturbance in gait was the result of hysteria. It was then suggested that she sit in the hot sun and she was told that she would not experience symptoms as she had in the past. She sat in the sun on 3 successive days and on the last day she was exposed to the sun for 2 hours. The observers noted that at the end of this time she was "literally drenched with perspiration." This case was reported as hysteria associated with an absence of sweating.

The case to be described below closely resembles that of Fog and illustrates the importance of bearing such a condition in mind when

dealing with individuals who cannot sweat. Every physician of wide experience can recall individuals who maintained that they were unable to perspire but who nevertheless when properly investigated revealed no abnormalities of their sweating mechanism.

**Case Report.** Mrs. E. H., a 49 year old white female, was admitted to the Tulane medical service of Charity Hospital on 7-15-43 with a complaint of "burning of the skin and fever." She stated that she had been perfectly well until 13 years previously when she fainted while scrubbing the kitchen floor. Immediately preceding this attack, she had noticed nervousness, dyspnea and a feeling of increased bodily heat. Since this episode, the patient had experienced frequent attacks of itching and burning of the skin associated with rise in temperature, at times to 102° F. These attacks occurred only during the summer months. She stated that her temperature rise was directly related to the hot weather and her degree of discomfort was directly proportional to the degree of environmental heat. There was no special daily variation and her symptoms were not related to the time of day but merely to changes in environmental temperature. Her most effective relief was found in frequent cold baths. Questioning revealed no antecedent disease which could be regarded as predisposing to her present symptoms except a history of typhoid fever during her youth. The patient had had several uneventful pregnancies.

**Physical Examination.** Blood pressure 120/80 mm. Hg, temperature 99° F., pulse rate 80 per min. The patient was a well-developed, well-nourished white female who appeared younger than the stated age of 49 years. The skin was essentially normal in appearance but quite wrinkled, especially on the face. There were many small, reddish papules on the medial aspect of both legs, extending up onto the thighs and involving both gluteal regions. The hair was normal in texture, amount and distribution.

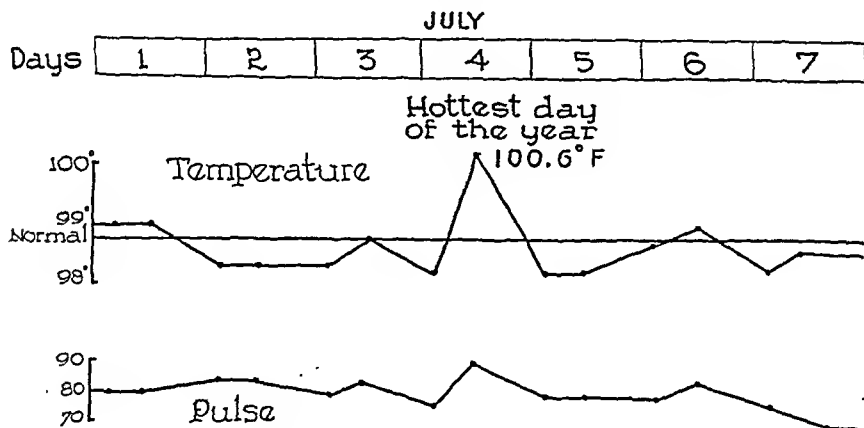


FIG. 1.—General acquired anhydrosis.

Examination of the eyes was negative as was examination of the nose and oral cavity. The thyroid gland was questionably enlarged. Examination of the chest and abdomen elicited nothing abnormal. Reflexes were physiologic. Vaginal examination gave normal findings. All laboratory tests gave results within the normal range, including complete urinalysis, blood picture, fecal examination, Kline and Kolmer serologic tests and repeated basal metabolic tests.

Prior to admission to Charity Hospital, the patient had sought medical attention from various physicians and according to her statement she was considered by them to be a psychoneurotic individual and was treated accordingly. After taking her history we were inclined to agree, but because of her com-

plaint of fever she was kept on the ward for observation. This policy of masterful neglect was rewarded by graphic evidence of hyperpyrexia which coincided with one of the hottest days of the year (Fig. 1). This observation led to detailed study of the patient's sweat mechanism.

**Methods of Study.** Through the courtesy of Dr. G. E. Burch<sup>4</sup> the patient was placed in an air conditioned room (temperature  $75^{\circ} \pm 1^{\circ}$  F.; relative humidity  $50 \pm 2\%$ ). The temperature was raised to  $120^{\circ}$  F. and the relative humidity to 75% and sweat was collected quantitatively from various areas of the body surface. She remained in this environment for 30 minutes, at the end of which time her rectal temperature reached  $105^{\circ}$  F. Visual and tactile examination of her skin failed to disclose to a number of observers any evidence of perspiration.

At the onset of the experiment the room temperature was  $75^{\circ}$  F. and the relative humidity 50%. In this environment 5.1 mg. of sweat was collected per 5 sq. cm. of skin per 10 minutes.\* The epigastrium was used as a site of collection. With the temperature of  $120^{\circ}$  F. and relative humidity at 75%, 9.7 mg. of sweat were collected.

Under similar conditions with normal subjects the results were as follows: With the environmental temperature at  $75^{\circ}$  F. and relative humidity at 75%, 5 mg. of sweat were collected from an area of epigastrium. With the environmental temperature at  $105^{\circ}$  F. and relative humidity at 75%, 50 mg. of sweat were obtained. For further study, dead skin taken from the epigastrium was subjected to an environmental temperature between  $55^{\circ}$  and  $60^{\circ}$  F. and only 3.8 mg. of fluid were obtained. With the temperature between  $66^{\circ}$  and  $86^{\circ}$  F. 5 mg. of fluid were obtained from the same area. With the temperature between  $87^{\circ}$  and  $104^{\circ}$  F., 5.9 mg. were obtained and with the temperature between  $105^{\circ}$  and  $115^{\circ}$  F., 7 mg. of fluid were obtained from this area of dead skin.<sup>4</sup>

These data would indicate that the diffusion rate of dead skin was not unlike that of our patient. It would appear then that the fluid collected from the patient contained little, if any, sweat gland sweat and that the fluid represented to a large extent water lost as a result of simple diffusion.

After the patient had recovered from this procedure and the temperature had returned to normal, her body was striped with tincture of iodine over which starch powder was applied. This technique for the demonstration of slight amounts of perspiration had previously been found to be adequate, giving a definite purple color wherever perspiration occurred. The patient was then given  $\frac{1}{2}$  gr. (0.013 gm.) of pilocarpine subcutaneously. This amount was sufficient to cause protracted vomiting, abdominal cramps and profuse salivation. Evidence of change in color of the stripes appeared only in the axillæ, in the perineal region and to a slight extent over the sternum.

It was decided that in order to study further this patient, skin biopsy should be performed.

\* Hereafter the units of sweat loss are expressed in mg./5 sq. cm. of surface area/10 minutes.

*Histologic examination* (courtesy of Dr. Charles E. Dunlap): Examination of the skin from the abdominal area revealed moderate atrophy of epithelium, subepithelial connective tissue and sudoriferous glands. Sections employing alloidin technique revealed 4 moderately atrophic sweat glands. The ostium of one gland appeared to be obstructed by a keratin plug. There was generalized atrophy and hyperkeratinization of the epidermis with focal variations in degree. Moderate hyaline degeneration of the subepithelial connective tissue was present. Repeated sections using the same technique revealed essentially the same anatomic changes (Fig. 2).

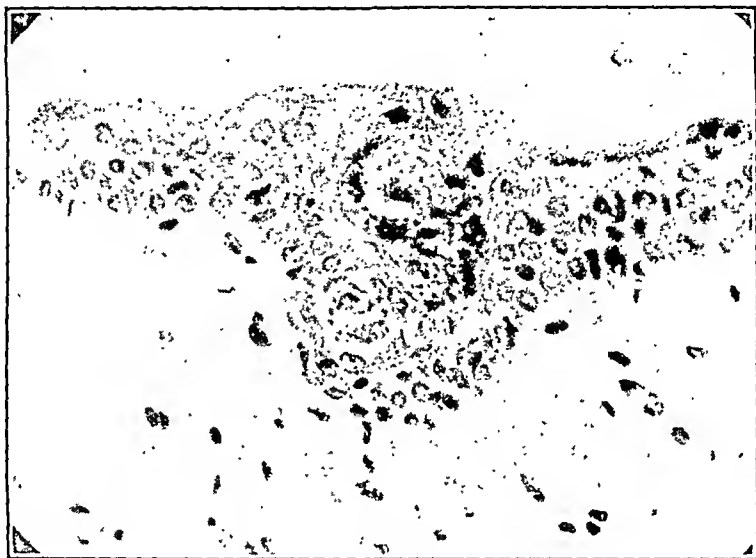


FIG. 2.—General acquired anhydrosis.

**Discussion.** Because one of us (H. T. E.) had previously had opportunity to study a family exhibiting hereditary ectodermal dysplasia,<sup>3</sup> our attention was drawn to this disturbance of sweat mechanism when the patient's temperature spiked to 100° F. on one of the hottest days of the year. Such a diagnosis was untenable in view of the fact that there was no substantiating familial history. This led to the detailed studies described above. It will be noted from these data that our patient presented findings consistent with the diagnosis of general acquired anhydrosis. It is of interest to hypothesize that the only predisposing causes that could be even considered in this and the other reported case were closely allied diseases: namely, paratyphoid fever in Fog's patient and typhoid fever in ours. However, in Fog's patient, the illness preceded the first symptoms by only 3 months while in our case there was a lapse of many years. Further dissimilarity is the fact that in our case, all the sweat glands examined revealed generalized atrophy. Although changes in the central heat centers cannot be discounted, it would appear from the information available that there were definite pathologic changes in the sweat glands which alone could explain the hyperpyrexia.

The patient has been followed for almost 2 years and when last seen reported that her ability to sweat had not returned. In spite of the fact that she had kept herself clad as cool and her environment as cool as possible, she still had the same complaints as when first seen.

**Summary and Conclusion.** A patient with general acquired anhidrosis is described. Various diagnostic procedures verified this diagnosis. Histopathologic examination of sections of skin revealed generalized atrophy of the sweat glands.

#### REFERENCES

1. BARRETT, A. M.: *Arch. Neurol. and Psych.*, 2, 628, 1919.
2. BECKMAN and HORTON: *Proc. Staff Meet. Mayo Clin.*, 12, 168, 1937.
3. BRUNG, F., and ENGELHARDT, H. T.: *Ann. Int. Med.*, 20, 140, 1944.
4. BURCH, G. E., and WINSOR, T.: *Arch. Int. Med.* (in press).
5. DE SILVA, P. C.: *Quart. J. Med.*, 8, 97, 1939.
6. EISENSTAEDT, J. S.: *J. Am. Med. Assn.*, 60, 27, 1913.
7. EMERSON, K., WALSH, F. B., and HOWARD, J. E.: *Ann. Int. Med.*, 4, 1256, 1941.
8. FOG: *J. Am. Med. Assn.*, 107, 2040, 1936.
9. GORDEN, W. H., and JORNISON, P. C.: *Ann. Int. Med.*, 5, 358, 1931.
10. HEBERT, J. M., and GARLAND, J.: *New England J. Med.*, 210, 784, 1934.
11. JACOBSEN, A. W.: *J. Am. Med. Assn.*, 90, 686, 1928.
12. MACKEE, G. M., and ANDREWS, G. C.: *Arch. Derm. and Syph.*, 10, 673, 1924.
13. SCHWARZ, E. G.: *South. Med. J.*, 28, 606, 1935.
14. SOECKERMANN, W. H.: *Arch. Derm. and Syph.*, 1, 396, 1920.
15. THANNHAUSER, S. J.: *J. Am. Med. Assn.*, 106, 908, 1936.
16. WECHSELMANN, W., and LOEWY, A.: *Berl. klin. Wehnschr.*, 48, Pt. II, 1369, 1911.
17. WEECH, A. A.: *Am. J. Dis. Child.*, 27, 766, 1929.

## POISONING BY HYDROQUINONE AND MONO-METHYL-PARAMINOPHENOL SULFATE

### REPORT OF 2 CASES WITH AUTOPSY FINDINGS

BY CAPT. IRVING ZEIDMAN, M.C.

AND

CAPT. RUDOLF DEUTL, M.C.

FIRST MOBILE SECT., 40TH STAT. HOSP., A.P.O. 366, C/O POSTMASTER, NEW YORK, N. Y.

PAST literature reveals reports of 3 cases of hydroquinone poisoning:<sup>1,4,7</sup> 2 of these include autopsy findings. No cases of poisoning from mono-methyl-paraminophenol sulfate have been reported. In view of the paucity of information on the toxic effects of these 2 compounds, so commonly used in photographic processes, it is thought that our experiences are worth reporting.

**Experimental Work.** Busatto<sup>2</sup> found that the subcutaneous injection of 0.16 to 0.17 mg. of hydroquinone per gram of body weight into white mice produced an acute syndrome divisible in 3 stages. The initial stage, lasting about 40 minutes, was characterized by markedly increased motor activity, hyperactive reflexes, sensitivity to light and acoustic stimulation, dyspnea and cyanosis; in addition, the tail often assumed a double-curved S-form, vertical to the back. The second stage revealed clonic convulsions increasing in frequency and intensity, and generally lasted 1 hour. The third stage, about 6 hours in duration, revealed a state of complete motor exhaustion, paralyses, diminu-

tion and almost disappearance of sensitivity and reflexes, semi-coma and death. The minimal lethal dose lay between 0.16 and 0.17 mg. per gm. of body weight. Larger doses diminished the duration of each period, and a dose about twice the minimal lethal dose eliminated the third stage entirely.

Oettel<sup>6</sup> studied hydroquinone poisoning in cats. Oral administration of 60 to 100 mg. of hydroquinone per kg. of body weight produced acute poisoning, characterized by increased sensitivity to physical stimuli, choreiform movements, subsequent partial paralyses, dyspnea, hypothermia, and edema of buccal mucosa, lips and conjunctiva. Death usually occurred in 7 to 36 hours. Blood changes were leukocytosis, reticulocytosis, and, after the first 24 hours, an increased cell fragility; rarely a trace of methemoglobin was found, but it was found in great quantity several hours after death. Urine revealed blackening several hours after exposure to air; albumen was always absent. Subacute hydroquinone poisoning was produced by the oral administration of 3 to 50 mg. per kg. of body weight and was characterized by dyspnea, hypothermia, alterations in muscle tonus, and hemolytic icterus. Ciaranfi<sup>3</sup> accurately determined the blood changes in subacute hydroquinone poisoning, and found a hyperchromic anemia, reticulocytosis, neutrophilic leukocytosis, eosinophilia, and in many cases myelocytes and metamyelocytes. The chronic form of hydroquinone poisoning revealed progressive anemia without icterus, reticulocytosis, sometimes leukocytosis, hypoglycemia; depigmentation of fur and a profound cachexia leading to death.

The mode of action of hydroquinone and related compounds is largely unknown. The concept of an internal asphyxia due to methemoglobinemia is not tenable, as methemoglobin is not detectable in significant quantities during life.<sup>1,4,6</sup> Possible but unproved, is that acute poisoning may lead to death by a direct action of the drug on the central nervous system, with respiratory and circulatory paralysis. Manifestations of subacute poisoning are obviously linked with the production of a hemolytic anemia with subsequent jaundice and reticulocytosis—whereas the anemia of the chronic type may be of a low grade hemolytic nature or secondary to depressed hematopoietic activity. There is no satisfactory explanation for the occasional hypoglycemia. Experimental evidence suggests that hydroquinone produces its toxic effects after being converted by oxidation to quinone.<sup>1,5</sup> Hydroquinone is eliminated rapidly from cats during the first 24 hours.<sup>6</sup>

**Previously Reported Cases.** Reinond and Colombics<sup>7</sup> report a case of suicide in which a 36 year old man took 12 gm. of hydroquinone; shortly thereafter, tinnitus, sleepiness, a suffocating sensation, and a swollen tongue were experienced. Physical examination revealed dyspnea, cyanosis and extreme somnolence. Improvement was marked after 24 hours. Urine examinations revealed a black color, which disappeared after the 4th day; a test for phenol in the urine was positive the first few days; albumen was negative. Blood changes consisted of hypoglycemia and hypercholesterolemia.



Halbron, Bosquet and Tiffenan<sup>4</sup> report a second case of poisoning from 5 gm. of hydroquinone and 4.5 gm. of benzcatechine in a negress. During the first 24 hours patient became unconscious, had convulsions and vomited black liquid; consciousness was recovered on the 2nd day. The urine and stool were colored black, the urine contained a trace of bile pigment, but no albumen or methemoglobin. At the end of the 4th day, icterus of the sclera was noticeable and gradually increased; the urine contained abundant bile pigment, bile salt, blood and albumen; a blood study revealed a white count of 50,000 leukocytes, 1.3 million, red blood cells and numerous normoblasts. Death occurred on the 12th day. At autopsy, the chief gross findings were petechiæ of the mucosa of the gastro-intestinal tract, and slight splenomegaly. Microscopically, the significant changes were in the liver; there was a hemorrhagic infiltration of perilobular regions, and biliary pigmentation of parenchymal cells.

Another suicide case is reported by Busatto<sup>1</sup> in a 29 year old female who took 6 gm. of hydroquinone and 2 gm. of metol. During the first 4 days, hypotension, weak pulse, cyanosis and slight icterus were manifested. On the 5th day, icterus increased markedly and hyperthermia developed; death occurred on the 6th day. Urine was normal in amount, brownish black after exposure to air, negative for sugar and albumen, positive for hemoglobin, and weakly positive for bile salts; granular and hyaline casts were contained in the urine specimen of the last day. Gross autopsy findings include icterus, bronchopneumonia, pulmonary edema and reddish brown urine in the bladder. Microscopic findings were cloudy swelling and fatty degeneration of the kidney, fatty degeneration of the liver, acute myocarditis, bronchopneumonia and pulmonary edema. No hydroquinone was found in urine or stools. The case corresponded to subacute hydroquinone poisoning in cats—that of hemolytic jaundice.

**Case Reports.\*** Two men took developing powder, mistaking it for Epsom salts. The subsequent clinico-pathologic pictures were almost identical. Therefore, both cases are reported in consolidated form, and any differences are noted.

On December 21, 1943 — and — each took about 15 gm. of developing powder, a mixture of hydroquinone and mono-methyl-*para*-aminophenol sulfate. Within 5 hours, — developed diffuse abdominal pain, vomiting and shock; the latter responded promptly to plasma therapy. — developed severe, diffuse abdominal pain, but no vomiting or immediate shock. Both were then admitted and treated in hospital. During their stay in the hospital, severe diffuse abdominal pain was the chief complaint, and their course was progressively downhill. Cyanosis, progressively deepening, tachycardia, melena and hematuria were observed; on the 3rd day — revealed a reversal of the pupillary response to light. Urinalysis, performed on each case immediately after micturition, revealed albumin, numerous erythrocytes, and free hemoglobin in the supernatant fluid after centrifugalization. — lived for 73 hours, — 92 hours, after the taking of the poison. Treatment consisted of intravenous glucose and plasma, sangstop, caffeine and camphor in oil.

**Necropsy Findings.** Macroscopic: Skin and sclera—icterus; cardiovascular system—fatty degeneration of heart (—), parenchymatous degeneration of heart (—), acute myocarditis, acute dilatation of right auricle and ventricle, atherosclerosis of aorta; respiratory system—acute passive congestion, acute

\* The histories and autopsy findings are so similar that the cases are reported together.

bronchitis, acute focal pulmonary arteritis (—), petechiæ of pleura; spleen—marked hyperemia, phagocytosis of erythrocytes; liver—acute passive congestion, bile pigmentation, phagocytosis of erythrocytes; abdominal cavity—petechiæ of peritoneum and panniculus adiposus, mesenteric lymph nodes—acute lymphadenitis; adrenals—parenchymatous degeneration; genito-urinary system—hemoglobinuric nephrosis; brain—petechiæ, acute passive congestion.

The bodies weighed about 130 pounds each, and were emaciated. The skin and scleræ of — were markedly icteric, whereas only the scleræ of — were yellow. The abdominal cavity was free of fluid and adhesions; the entire visceral and parietal peritoneum and the panniculus adiposus were studded with pin-point red spots; the large intestine was collapsed. Pleural cavities were free of fluid, and the pericardial cavity contained about 20 cc. of pink, slightly cloudy fluid.

The pleura contained scattered pin-point red spots, and was smooth and glistening. The parenchyma of the lung was tawny in color and crepitant, save in the lower lobes where it was red, oozed considerable serosanguinous fluid, and revealed diminished crepitation. Bronchi contained serosanguinous fluid. Pulmonary vessels were not remarkable.

The heart weighed about 425 gm. There was moderate enlargement of the right sides, and, on opening, dilatation of the corresponding chambers. The pericardium was not remarkable. The myocardium was reddish brown and firm; in the case of —, the myocardium revealed fine yellow streaking most prominent in the papillary muscles. The endocardium and valves of — were yellow-tinged. Measurements of valves and ventricular thicknesses were within normal limits. The entire cardiovascular system was filled with tawny-brown clotted blood; the clot was easily removed.

The livers revealed slight enlargement and weighed about 1550 gm. each. Free margins were rounded. Sections displayed golden-brown, slightly bulging parenchyma. An iron stain of the tissue was negative.

Gall bladder, pancreas and adrenals were not remarkable.

Both spleens were firm, and about  $1\frac{1}{4}$  times normal size, and weighed approximately 250 gm. each. Capsules were thin and smooth. On section, the parenchyma was firm, non-bulging, and uniformly reddish purple.

The kidneys of both cases were slightly enlarged; each kidney weighed approximately 200 gm. Capsules stripped with ease, revealing smooth cortical surfaces. On section, the parenchyma bulged, oozed considerable blood, and was dark red in color. At the cortico-medullary junctions there was heavy reddish purple mottling which, in the immediately overlying cortex, assumed a striated, radiating pattern, perpendicular to the capsule. Cortical thickness over pyramids was uniformly 8 mm. Cortical vascular striations were obscure. Pelves and ureters were not remarkable. The bladders contained about 100 cc. of red, cloudy urine; the mucosæ revealed no abnormalities. Prostates, testes and epididymis were not remarkable.

The gastro-intestinal tracts displayed no abnormalities other than a deep green stain of the fecal contents. Mesenteric lymph nodes were slightly enlarged. Sections revealed uniformly pink parenchyma.

The brains revealed injection of the meninges, pink spinal fluid in the ventricles, and scattered pin-point red spots throughout the white matter of the cerebral hemispheres.

Microscopic: The chief pathologic findings were centered in the kidneys, liver, spleen, heart, lung and brain. Almost exact changes were presented in both cases.

In the kidney peritubular and glomerular capillaries were markedly dilated. Bowman's spaces were frequently filled with homogeneous eosinophilic material containing an occasional erythrocyte; the cellular pattern of glomeruli and their capsules was not disturbed. Cells of convoluted tubules were swollen, hazy in outline, and loaded with large intracytoplasmic eosinophilic, refractile, hyaline droplets. Henle's loops, and collecting tubules of cortex and medulla, were filled with deep red, homogeneous and granular casts which contained an occasional incorporated erythrocyte. The interstitial tissue and large blood-vessels revealed no abnormalities.

The liver revealed dilatation of central veins and sinusoids. Küpfer cells were prominent, and occasionally contained an erythrocyte or a few scattered coarse, brown, intracytoplasmic granules. The cytoplasm of parenchymal cells in the center of tubules was filled with fine, golden-brown granules. Perilobular regions revealed no abnormalities.

Venous sinuses of the red pulp of the spleen were markedly dilated, and filled with erythrocytes; in some areas the sinus architecture was obscured by the marked accumulation of erythrocytes. Endothelial cells of the red pulp and, occasionally, monocytes of the Malpighian follicles contained an erythrocyte in the cytoplasm. No other abnormalities were observed.

Myocardial fibers of the heart revealed swelling, partial loss of transverse striations, sarcoplasmic vacuolization, and occasional elongation and widening of nuclei. There were focal accumulations of plasma cells and polymorphonuclear leukocytes in the interstitium, most prominent in the papillary muscle and subendocardial region.

Alveolar spaces of the lung contained homogeneous eosinophilic material and a rare neutrophil. Interstitial capillaries were dilated, and the interstitium contained occasional erythrocytes and rare neutrophils. Bronchiolar mucosæ revealed capillary dilatation and neutrophilic infiltration. In the case of — one small artery contained numerous neutrophils in its intima, and its endothelial lining had disappeared.

The brains revealed focal parenchymal collections of erythrocytes with surrounding rims of separated glial fibers. Capillaries were dilated and occasionally filled with homogeneous eosinophilic material. Virchow-Robin spaces sometimes contained a few round cells and Gitter cells. Scattered neurons were swollen, and their outlines were hazy.

**Discussion.** The autopsy findings and clinical history indicate that both cases developed an overwhelming hemolytic anemia with jaundice in response to intoxication with hydroquinone and mono-methyl-paraminophenol sulfate. In both cases, the indications for this conclusion were marked engorgement of the venous sinuses of the splenic red pulp, phagocytosis of erythrocytes in the spleen and liver, marked nephrosis and heavily pigmented casts in the kidney, bile pigmentation (microscopic) of liver, hemoglobinuria and jaundice (marked in 1 case, slight in the other). The 2 cases correspond to subacute hydroquinone poisoning in cats<sup>3,6</sup> and to 2 reported cases.<sup>1,4</sup> The rôle of methemoglobinemia in causing the deaths is hard to evaluate. The tawny color of the clots in the cardiovascular system suggest methemoglobin formation, but Oettel<sup>6</sup> has found that in cats the great majority of the methemoglobin change occurs after death; both posts were performed approximately 12 hours after death. Bladder urine of patient revealed the presence of reducing substances by simple chemical tests, suggesting that the toxic agents were still acting at the time of death.

**Summary.** 1. Experimental work on the effect of hydroquinone in animals is summarized.

2. Three previously reported cases of hydroquinone poisoning are reviewed.

3. Two new fatal cases of poisoning from hydroquinone and mono-methyl-paraminophenol sulfate are reported.

4. It is concluded that the chief pathologic changes produced by the 2 compounds were attributable to a hemolytic jaundice.

The authors wish to acknowledge their indebtedness to Lt. Col. Balduin Lucké and Dr. W. A. Sawyer for their encouragement to report the cases, and to the Army Medical Library which sent a partial bibliography overseas. Papers 3 to 6 in References were utilized indirectly from other papers listed.

## REFERENCES

1. BUSATTO, S.: *Deutsch. Ztschr. f. d. ges. gerichtl. Med.*, 31, 285, 1939.
2. BUSATTO, S.: *Arch. di antropol. crim.*, 60, 620, 1940.
3. CIARANFIE: *Bull. Soc. ital. biol. sper.*, 8, 147, 1933.
4. HALBRON, D., BOSQUET, A., and TIFFENAU, P.: *Bull. Soc. méd. d. hôp. de Paris*, 55, 1596, 1931.
5. LABES: *Arch. f. exp. Path.*, 139, 120, 146, 44, 1929; 152, 111, 1930.
6. OETTEL: *Arch. f. exp. Path.*, 183, 319, 1936.
7. REMOND, A., and COLOMBIES, H.: *Ann. de méd. Leg.*, 7, 79, 1927.

## THE XIPHOSTERNAL CRUNCH AND ITS INCIDENCE IN HEALTHY INDUCTEES

BY MYER SOLIS-COHEN, M.D.

PHILADELPHIA, PA.

IN about one-fifth of healthy men a crunching sound is heard constantly or frequently over the ensiform cartilage and the lower portion of the sternum and to their left. This sound is of no pathologic significance and its cause is not known. Yet it not infrequently is mistaken for the murmur of mitral insufficiency, in consequence of which men have been denied life insurance or have been rated up, have been refused employment, have been rejected by the armed forces, and have been subjected to unnecessary treatment with its accompanying expense, trouble and anxiety.

This crunch is mentioned in only a very few of the books on cardiology, physical diagnosis and medicine and is seldom referred to in published articles on the heart and the heart sounds. Nevertheless, during the past century and a quarter a number of physicians have described this phenomenon, while others have noted sounds which probably are identical with it.

**References to the Xiphosternal Crunch.** In 1819 Laennec<sup>39</sup> wrote of a buzzing heard at the lower part of the sternum and between the cartilages of the left 6th and 7th ribs, and in 1826,<sup>40</sup> among the phenomena which might be confused with true cardiac murmurs, called attention to a metallic click and to a creak, which formerly he had mistaken for a sign of pericarditis. Bouillaud<sup>12</sup> in 1835 and Aram<sup>4</sup> in 1843 referred to the first mentioned sound as a metallic clacking, the latter regarding it as of little diagnostic importance. Latham<sup>41</sup> in 1847 noted a scratch or scrape under the lower part of the sternum in healthy individuals. A chisel-sound at the lower end of the sternum was found by Brown<sup>14</sup> in 1856 to be of frequent occurrence in healthy persons.

In 29 of 111 parturient and puerperal women, Money<sup>52</sup> in 1882 heard just above and to the left of the ensiform cartilage a systolic friction-like sound that sounded quite superficial and was short, high-pitched, and rather stiff in quality. A grating or coarsely rubbing sound in the tricuspid area was reported by Russell<sup>60</sup> in the same year as occurring in a number of cases with debility. Sansom<sup>61</sup> 10 years later called attention to rough, scraping, seemingly very superficial,

systolic sounds, heard over the tricuspid area and the right ventricle, in conditions that deviated in no notable way from the standard of health.

In 1897 Broadbent<sup>13</sup> stated that a muscial tricuspid systolic murmur may sometimes be heard over a limited area, but seldom had any important significance. Three years later Abrams<sup>2</sup> referred to a rough or whizzing murmur loudest at the 4th left interspace close to the sternum. Hare<sup>26</sup> in the following year described a peculiar vibrating sound occurring with systole and heard best from 1 inch to the right of the sternum to 1 inch to the left of the nipple, on the nipple level, sometimes dry, like a pericardial friction sound, which he was confident it was not. Eighteen years later,<sup>27</sup> in referring to what was probably the same sound, he spoke of it as a short flapping or tapping sound, single or double, but said it was of no significance.

Osler,<sup>56</sup> in discussing Hare's first paper, mentioned two sounds that sometimes worried and sometimes puzzled him. In the majority of healthy hearts, as he moved his stethoscope from the apex to the sternum, he heard a peculiar and remarkable crunching sound. Also at the apex he frequently heard a little grating sound, much like a fine pericardial friction, yet not having the rubbing nature of that sound. Also in 1901 Colbeck<sup>16</sup> discussed a peculiar form of friction sound, accompanying systole, sometimes heard at the level of the 5th and 6th intercostal spaces, close to the left sternal edge and over the base of the ensiform cartilage, commonly observed in downward displacement of the heart due to emphysema, but also present under apparently normal conditions.

Forty-two years ago the writer<sup>64</sup> described in detail a xiphosternal crunching sound, heard over the lower sternum and a little to its left, and gave the first review of the literature on the subject. Six years later<sup>65</sup> he published an analysis of 63 cases that exhibited this sound, studied with regard to its time, position and boundaries, and the effect upon it of body position, exercise, pressure of the stethoscope, size of the heart, condition of the cardiac muscle, and other factors. Satterthwaite<sup>62</sup> in 1905 spoke of a tricuspid systolic murmur occurring in anemia. Three years later Porter<sup>59</sup> expressed his belief that what had generally been regarded as a tricuspid murmur is a type of murmur which to his mind was very common. In a large percentage of cases he found this murmur to exist without any symptom. Benedict<sup>9</sup> in 1910 noted the xiphosternal crunch in several cases and suggested its identity with the thump, crunch, swish, or indescribable murmur, synchronous with the heart beat, heard over a distended stomach. In 1914 Blumer<sup>11</sup> pointed out a physiologic difference in the quality of the heart sounds underneath and in the neighborhood of the sternum, as compared with the sounds over the rest of the heart. This superficial scratching sound he regarded as a normal phenomenon which may be mistaken for a pathologic sound and give rise to errors in diagnosis.

King<sup>34</sup> in 1919 and again in 1932,<sup>35</sup> 1939<sup>36</sup> and 1940<sup>37</sup> mentioned a superficial crunching sound at the lower left border of the sternum,

heard in normal persons, which had been mistaken for an organic murmur<sup>34</sup> and for a true pericardial rub.<sup>37</sup>

Meyer<sup>51</sup> in 1921 discussed systolic murmurs localized at the base of the xiphoid appendix, not propagated the length of the costal border, and others which were parasternal, generally on the left at the inner extremity of the 4th interspace or of the 4th rib, extending over a more or less extended area, transmitted a little toward the apex, which must be differentiated from the murmur of tricuspid functional insufficiency. Norris<sup>55</sup> asserted in 1924 that in a considerable number of perfectly healthy individuals the heart sounds heard just over the ensiform cartilage and in its immediate vicinity have a peculiar harsh, scratching, scraping, or crunching quality closely resembling a pericardial friction sound, its importance lying in the fact that it may readily be mistaken for a pericardial friction or a mitral murmur. Thirteen years later Fishberg<sup>19</sup> referred to a not uncommon crunching sound which is confused with the murmur of relative tricuspid insufficiency.

In 1940 Anderson<sup>3</sup> said that at times a rasping, almost musical murmur, following the first sound, can be heard at the left sternal border at the level of the 4th or 5th rib. Haskin<sup>29</sup> in 1942, examining recruits, found functional heart murmurs extremely common, occurring chiefly at the apex, but also down the left side of the sternum. He labels as exocardial certain murmurs usually heard down the left side of the sternum, but occasionally at the apex, which are harsh and often loud, superficial and not conducted, and are sometimes misdiagnosed as congenital heart lesions. Writers who refer to the xiphosternal crunch, but who do not mention having heard it, are Bennett<sup>10</sup> (1906), Askenstedt<sup>5</sup> (1913) and Lyon<sup>47</sup> (1941).

**References to Sounds That May Be Identical With the Xiphosternal Crunch.** In addition to the references given above, a number of writers have described murmurs which are probably identical with the xiphosternal crunch. These include: the friction character assumed in some persons by the element of impulsion in the first heart sound and the slight rubbing or grazing sound accompanying systole, noted by Flint;<sup>20</sup> the aftertone or echo, heard by Hayden<sup>30</sup> both over the base of the xiphoid cartilage and over the 6th and 7th costal cartilages about 1 inch to the left of the sternum; the superficial murmur perceived by Labougle,<sup>38</sup> best on a line going from the apex to the xiphoid, and heard also, according to him, by Lamacq and others; the permanent tricuspid bruit, referred to by Pitt;<sup>58</sup> the murmurs in some of the cases reported by Ellis;<sup>18</sup> the systolic tricuspid murmur with absence of symptoms, other signs and etiology, described by Laubry;<sup>42</sup> the short, superficial, systolic, precordial murmurs with a scraping quality, of which Lendon<sup>43</sup> wrote; the coarse limited pericardial rub which to Carlisle<sup>15</sup> sounds more like a murmur; and the grating sound of the first tone occurring in the rapid heart of the apprehensive individual, to which Markson and Gethner<sup>49</sup> refer.

**Possible Mistaking of the Xiphosternal Crunch for the Murmur of Relative or Functional Tricuspid Insufficiency.** It is likely that the

xiphosternal crunch is sometimes mistaken for the murmur of relative or functional tricuspid insufficiency, especially as in their reports of the latter many writers make no mention of an accompanying pulsation of the veins in the neck or of an enlarged, tender and pulsating liver. Tricuspid regurgitation seems to have been found much more frequently by the older writers than by physicians at the present time. Penfold<sup>57</sup> concluded that it occurs in the majority of men and may be looked upon as physiologic. Gibson<sup>24,25</sup> regarded it as the most common valvular affection, although he admitted<sup>25</sup> that in a very large proportion of cases auscultation furnishes the sole evidence of the disease and that there may not be any perceptible widening of the orifice. Mackenzie<sup>48</sup> found incompetence of the tricuspid valve so common that he was inclined to look upon the valves as being barely able to close the orifice perfectly.

On the other hand, Babcock,<sup>7</sup> admitting that there may at times be slight leaks that are not considerable enough to produce positive venous pulse in the cervical veins and liver, regarded this merely as a matter of conjecture. He was unwilling to accept the presence of systolic whiff in the tricuspid area as conclusive evidence of leakage at this orifice, and said one might argue that the murmur is due to some other condition than actual regurgitation.

**Probable Confusion of the Xiphosternal Crunch With Cardiorespiratory Murmurs.** In all probability many physicians have looked upon the xiphosternal crunch as a cardiorespiratory murmur, notwithstanding the fact that it fulfils none of the criteria of the latter, although its intensity sometimes varies with the different phases of respiration. Moreover in many books and articles the cardiorespiratory is the only accidental murmur mentioned. Neuhof<sup>53,54</sup> even says that the so-called cardiorespiratory murmur may be rough and loud, and be transmitted along the left sternal border and lower precordium as a somewhat superficial, squeaky sound, resembling a friction sound. Dressler<sup>17</sup> likewise spoke of cardiopulmonary murmurs heard in the apical region or near the left sternal border, which resemble some intracardiac murmurs.

**Xiphosternal Crunch Mistaken for the Murmurs of Mitral Incompetency and of Congenital Heart Disease and for Pericardial Friction.** Undoubtedly the xiphosternal crunch has been mistaken for the murmur of mitral insufficiency. The writer has seen such errors made by competent internists and cardiologists. Others have referred to similar mistakes.<sup>9,11,13,22,34,40,55,57</sup> This is what makes recognition of the nature of the phenomenon so important.

Differentiation is rendered more difficult by the facts that in some cases of mitral incompetency the murmur has its maximum intensity in the tricuspid area<sup>7,16</sup> or along the left sternal border,<sup>16,18,33,46,50,63,68,69,72</sup> and may be transmitted to the ensiform cartilage,<sup>1</sup> while, on the other hand, a murmur originating in the tricuspid area may be transmitted to the apex<sup>13,68</sup> and occasionally has its maximum intensity just to its inner side.<sup>13</sup> Harris<sup>28</sup> found it often difficult to say whether a systolic murmur has originated at the tricuspid or has been transmitted from another area.

According to Broadbent,<sup>13</sup> when a murmur heard at the apex is lost immediately to the left of the beat, while it is audible between the apex and the lower end of the sternum, its seat of production is at the tricuspid, and not at the mitral orifice. Benedict<sup>9</sup> questioned whether some of the common statements regarding the development of functional mitral leakage under strain may not depend upon the incorrect interpretation of the xiphosternal crunch. Haskin<sup>29</sup> referred to this phenomenon being mistaken for the murmur of a congenital heart lesion. The xiphosternal crunch has sometimes been diagnosed as the friction of a pericarditis<sup>37,40,55</sup> and has been described as a friction sound.<sup>16,26,52,56</sup>

**Failure of Most Clinicians to Recognize the Xiphosternal Crunch.** Despite the references to the xiphosternal crunch in medical literature during the past 125 years, it is recognized by few physicians and has been ignored by most writers on cardiology, physical diagnosis, and general medicine. When faint, it may easily be overlooked, but when moderate, and especially when marked, it is readily heard.

It naturally will be missed by those physicians, including some cardiologists and internists, who seldom listen over the xiphoid cartilage and lower sternum, probably because significant murmurs are rarely heard there. Freeman and Levine,<sup>21,45</sup> in their study of 1000 consecutive "non-cardiac" cases, to determine the clinical significance of the systolic murmur, and Gibbes,<sup>23</sup> in his investigation of heart murmurs, heard in 1166 consecutive examinations, refer only to the apex and the base of the heart. Similarly systolic murmurs were divided by Hunt<sup>31</sup> into those best heard over the base of the heart and over the apex.

In the writer's opinion, the failure of most cardiologists and internists to notice the xiphosternal crunch is due to the fact that their ears have become so trained to recognize pathologic sounds and to ignore all other sounds which their experience has taught them have no pathologic significance, that the latter sounds, when heard, are not impressed on their field of consciousness. Von Jürgensen<sup>32</sup> similarly explained why a person with an acute ear, but without an intimate knowledge of the heart, can hear "murmurs" more easily than one with an experienced ear, which from the first is accustomed to exclude the unessential features of the sensory impression, with the result that these features of it escape his observation. Gibson<sup>25</sup> said that tricuspid incompetence is so commonly found during the examination of patients who suffer from diseases of the most varied kind, that it frequently passes unrecorded.

Wolferth and Margolies<sup>70</sup> complain that "extra" heart sounds constitute a very common auscultatory finding and yet comparatively little is said about them in the various standard works on physical diagnosis. Nevertheless, these authors fail to mention the xiphosternal crunch in either of their articles on extra heart sounds.<sup>70,71</sup>

**Characteristics of the Xiphosternal Crunch.** The characteristics of the xiphosternal crunch are not always the same. While frequently likened to a crunch,<sup>9,19,34,55,56,64,66</sup> the phenomenon has also been de-



scribed as a rubbing,<sup>16,26,60,64</sup> brushing,<sup>64</sup> scraping,<sup>41,55,61,64</sup> grating,<sup>56,60</sup> scratching,<sup>11,34,55,60</sup> rasping,<sup>3</sup> chisel-sound,<sup>14,66</sup> buzzing,<sup>39</sup> flapping,<sup>27,66</sup> puff,<sup>66</sup> squeal,<sup>65</sup> squeak,<sup>34</sup> click,<sup>4,12,16,40,64</sup> metallic click or tinkling,<sup>4,12,40</sup> clacking,<sup>4,12,66</sup> creak,<sup>40</sup> whizzing,<sup>2</sup> tapping,<sup>27</sup> murmur,<sup>11,34,40,51,59,62,66</sup> gastric tinkle,<sup>30</sup> aftertone or echo,<sup>30</sup> reduplication,<sup>16,66</sup> coin sound,<sup>26</sup> the word "ching,"<sup>26</sup> friction,<sup>11,16,26,34,52,55,56,64</sup> and a vibrating,<sup>26,66</sup> and as high-pitched,<sup>52,64</sup> rough,<sup>2,61,64</sup> superficial,<sup>11,29,34,52,55,61,64</sup> dry,<sup>26</sup> stiff,<sup>26,62</sup> harsh,<sup>29</sup> short and rough,<sup>61</sup> short and quick,<sup>26</sup> musical,<sup>3,13</sup> and extra-cardial.<sup>3,14,29</sup>

The sound has been compared to that made by a foot crunching in soft snow,<sup>64</sup> by striking the clasped hands against the knee,<sup>26,35,64</sup> by a chisel or short plane used forcibly across the end of a piece of timber,<sup>14</sup> by a file drawn over wood,<sup>39</sup> by the rubbing together of two pieces of velvet,<sup>64</sup> by drawing a cork out of a bottle,<sup>64</sup> by allowing a stiffly starched cuff to rub slightly against the other, while they are on the wrist,<sup>26</sup> and to a motor-knock,<sup>26</sup> to the creak of leather of a new saddle under the rider,<sup>40</sup> and to the sound heard when one places the palm of the hand over the ear and percusses the occiput with the end of the index finger.<sup>40</sup>

The xiphosternal crunch is regarded as accompanying systole<sup>14,16,26,52,61</sup> by many, although some say it may be systolic,<sup>11,26</sup> diastolic,<sup>34,55</sup> or both. In the writer's experience the majority has been systolic.

The phenomenon has been observed by Blumer<sup>11</sup> in all ages after infancy but by the writer chiefly in adults. Other observers fail to mention age.

In many cases the sound is increased by leaning forward,<sup>11,34,55,65</sup> by exercise,<sup>2,65</sup> and by nervousness, excitement or fear,<sup>2,26</sup> and is diminished on lying,<sup>34,65</sup> when it may even disappear.<sup>2,34,65</sup>

The different phases of respiration may or may not affect it, but it never is present only during the respiratory motion.

The area over which the crunch is heard varies greatly in extent, usually being greater when the sound is loud. In Blumer's<sup>11</sup> cases the area of maximum intensity was 13 by 9 cm. in the average adult and 7 by 4 cm. in children.

**The Cause of the Xiphosternal Crunch.** The origin of the xiphosternal crunch is unknown, although various explanations have been suggested.

The cause has been regarded by some as endocardial, such as vibrations of the chorda tendineæ produced by imperfect contraction of their muscular attachments,<sup>26</sup> permanent lack of tone,<sup>58</sup> and congenital perforation of the aortic valve.<sup>59</sup> The phenomenon has been regarded as a valve sound,<sup>26,38</sup> a cardiomuscular sound,<sup>2,66</sup> and a drawing out of the scratch of the second aortic sound.<sup>34</sup>

A number of observers have believed the cause to be in the pericardium, including a fibrous patch on the pericardium,<sup>52</sup> fibrous patches plus toxemia,<sup>14,60</sup> bubbles of air in the pericardium,<sup>40</sup> rubbing of the visceral over the parietal lamina of the pericardium<sup>52</sup> and localized precordial roughening.<sup>29</sup> Benedict<sup>9</sup> thought the crunch to be of cardiopulmonary origin, due to a direct compressive action of a tilted

or displaced heart against the lung, producing an audible current of air from the vesicles into the bronchial tubes.

Other explanations are: friction of the heart against the chest wall,<sup>3,12,34</sup> the crowding of an enlarged heart in the inferior mediastinum,<sup>40</sup> downward displacement of the heart due to emphysema,<sup>16</sup> mediastinal emphysema—the air in the tissues causing a crepitant sound,<sup>60</sup> movement of the xiphoid,<sup>19</sup> changes in the tension of the loose cellular tissue in the sterno-pericardial ligament, which binds the anterior surface of the pericardium to the posterior thoracic wall and which may be affected by the movements of the heart,<sup>11</sup> and gastric resonance imparted to the right ventricle of the heart through the diaphragm.<sup>9,30</sup>

**The Incidence of the Xiphosternal Crunch in Healthy Men (Inductees).** Blumer<sup>11</sup> regards the xiphosternal crunch as a normal phenomenon. He, Osler,<sup>56</sup> Brown,<sup>14</sup> and Norris<sup>55</sup> have found it of frequent occurrence in health. It has also been observed in healthy persons by Sansom,<sup>61</sup> Colbeck,<sup>16</sup> King<sup>34</sup> and the writer. No attempt has been made heretofore, however, to find out how frequently it occurs in persons in good health.

**Procedure.** In order to determine the incidence of this phenomenon in healthy men the writer has recorded its occurrence in 5000 consecutive examinations of inductees, noting the intensity and transmission of the sound and the age, development and pulse rate of those exhibiting it.

The men were seated when examined and in most instances were not made to lean forward, lie down or exercise.

Of 4982 men studied, 887 (17.8%) showed the xiphosternal crunch. The last 3000 were examined more carefully than the preceding 2000 and the writer's ear probably had become more acutely sensitive to the sound. In 660 (21.1%) of these 3115 men the crunch was heard. More careful notes were made in this latter group as to accompanying conditions.

In these 660 cases the crunch was slight in 43.3%, moderate in 35.7% and marked in 21%. The cases where the crunch was slight might easily be missed by one not accustomed to the sound. The marked crunch is the one that is most likely to be mistaken for a murmur (Table 1).

TABLE 1.—CHARACTERISTICS OF XIPHOSTERNAL CRUNCH

*Incidence:* 660 cases found in 3115 examinations (21.1%)

*Degree:* Slight in 43.3%; moderate in 35.7%; marked in 21%

*Diagnosed as murmurs:* Mitral, 24 (3.6%); functional, 10 (1.5%)

*Sound transmission:* None, 18.2%; to the left, 81.8% (midprecordium, 9.3%; apex, 1.7%)

Of these 660 crunches, 24 (3.6%) are known to have been diagnosed as organic mitral murmurs and 10 (1.5%) as functional murmurs (Table 1).

The crunch was heard only over the sternum and ensiform in 18.2% of these cases and was transmitted to the left in 81.8%, being heard as far as the mid-precordium in 9.3% of the latter and as far as the apex in 1.7% (Table 1).

The body development of those exhibiting this phenomenon was not found to be poor (Table 2), although some attribute it to the presence of a thin chest wall or of a funnel-chest. The unusually high pulse rate (Table 3) was probably due to excitement incident to the examination. Nearly all those with pulse rates above 100 were made to lie down for varying periods before the final count was made.

TABLE 2.—AMOUNT OF BODY DEVELOPMENT  
(In 749 men exhibiting crunch)

	Per cent
Poor . . . . .	3.4
Fair . . . . .	16.6
Good . . . . .	80.0

TABLE 3.—SITTING PULSE RATE  
(In 733 men exhibiting crunch)

Rate	Per cent
70 or less . . . . .	6.2
71-80 . . . . .	15.0
81-90 . . . . .	25.3
91-100 . . . . .	39.3
101-110 . . . . .	5.6
111-120 . . . . .	6.0
Over 120 . . . . .	2.4

**Summary.** In a little over one-fifth of healthy men (inductees) a crunching sound is heard over the lower sternum and the ensiform cartilage, accompanying one or both sounds of the heart and occurring chiefly during systole. The intensity of this sound is slight in a little less than half the cases, moderate in a little more than one-third and marked in slightly more than one-fifth. This crunch is confined to the sternum and ensiform in a little less than one-fifth of the cases and is transmitted to the left in slightly more than four-fifths, being heard as far as the apex in slightly less than a tenth of the latter.

In men the sound apparently bears no relationship to general development or pulse rate.

Apparently the crunch has no pathologic significance.

The importance of its recognition lies in its sometimes being regarded as an organic or congenital heart murmur or as a pericardial friction.

Although this sound has been reported on a number of occasions from 1819 to the present time, it seldom is referred to in books or articles on cardiology, medicine or physical diagnosis and is recognized by few clinicians.

#### REFERENCES

1. ABRAHAMS, R.: *The Post-Graduate*, 34, 527, 1908.
2. ABRAMS, A.: *Diseases of the Heart: Their Diagnosis and Treatment*, Chicago, Engelhood, 1900.
3. ANDERSON, W.: *Physical Diagnosis*, Philadelphia, Lea & Febiger, 1940.
4. ARAM, F.-A.: *Manuel Pratique des Maladies du Cœur et des Gros Vaisseaux*, Paris, Rouvier, 1842.
5. ASKENSTEDT, F. C.: *Kentucky Med. J.*, 11, 505, 1913.
6. BABCOCK, R. H.: *J. Am. Med. Assn.*, 70, 355, 1918.
7. BABCOCK, R. H.: *Diseases of the Heart and Arterial System*, New York and London, Appleton, 1903.
8. BARKER, L. F.: *Canada Lancet*, 51, 545, 1918.
9. BENEDICT, A. L.: *Arch. Diag.*, 3, 340, 1910.

10. BENNETT, C. D.: J. Med. Soc. New Jersey, 2, 359, 1906.
11. BLUMER, G.: Arch. Int. Med., 14, 605, 1914.
12. BOUILLAUD, J.: *Traité Clinique des Maladies du Cœur*, Paris, Baillière, vol. 1, 1835.
13. BROADBENT, W. H., and BROADRENT, F. H.: *Heart Disease: With Special Reference to Prognosis and Treatment*, London, Baillière, Tindall & Cox, 1897.
14. BROWN, F. J.: Assn. Med. J., N. S., 4, 384, 1856.
15. CARLISLE, G. L.: Dallas Med. J., 26, 42, 1940.
16. COLBECK, E. H.: *Diseases of the Heart*, London, Methuen, 1901.
17. DRESSLER, W.: *Clinical Cardiology With Special Reference to Bedside Diagnosis*, New York and London, Hoeber, 1912.
18. ELLIS, R.: Med. Rec., 74, 145, 1908.
19. FISHBERG, A. M.: *Heart Failure*, Philadelphia, Lea & Febiger, 1937.
20. FLINT, A.: *Practical Treatise on the Diagnosis, Pathology and Treatment of Diseases of the Heart*, Philadelphia, Blanchard & Lea, 1859.
21. FREEMAN, A. R., and LEVINE, S. A.: Ann. Int. Med., 6, 1371, 1933.
22. GAIRDNER, W. T.: *Clinical Medicine: Observations Recorded at the Bedside With Commentaries*, Edinburgh, Edmonston & Douglas, 1862.
23. GIBBES, J. H.: Am. Heart J., 4, 305, 1929.
24. GIBSON, G. A.: *Diseases of the Heart and Aorta*, Edinburgh and London, Pentland, 1898.
25. GIBSON, G. A.: *Diseases of the Endocardium*, in G. A. Gibson's *Practice of Medicine*, Philadelphia, Lippincott, vol. 2, 1901.
26. HARE, H. A.: Trans. Assn. Am. Phys., 16, 1, 1901.
27. HARE, H. A.: U. S. Naval Bull., 13, 1, 1919; Med. Ins. and Health Conservat., 28, 294, 1919.
28. HARRIS, I.: *Diseases of the Heart: A Handbook for Students and Practitioners*, London, Baillière, Tindall & Cox, 1922.
29. HASKIN, T. J.: Post-Grad. Med. J., 18, 3, 1942.
30. HAYDEN, T.: *The Diseases of the Heart and of the Aorta*, Philadelphia, Lindsay & Blakiston, Part I, 1875.
31. HUNT, G. H.: Clin. J., 61, 349, 1922.
32. VON JÜRGENSEN, T.: *Valvular Disease*, in *Diseases of the Heart* by Th. von Jürgensen, L. von Schrötter and L. Krebl; in *Nothnagel's Encyclopedia of Practical Medicine*, Amer. ed., Philadelphia and London, Saunders, p. 330, 1908.
33. KELLY, A. O. J.: *The Practice of Medicine*, Philadelphia and New York, Lea & Febiger, 1910.
34. KING, J. T.: Arch. Int. Med., 24, 89, 1919.
35. KING, J. T., JR.: *Practitioners Library of Medicine and Surgery*, New York and London, Appleton, 2, 25, 1932.
36. KING, J. T., JR.: *Cyclopædia of Medicine, Surgery and Specialties*, Philadelphia, Davis, 3, 775, 1939.
37. KING, J. T., JR.: W. D. Stroud's *The Diagnosis and Treatment of Cardiovascular Disease*, Philadelphia, Davis, 1, 472, 1940.
38. LABOUGLE, F. E. J.: Arch. de méd. et de pharm. mil., 45, 393, 1905.
39. LAENNEC, R. T. H.: *De l'Auscultation Mediate*, Paris, Brosson et Chaude, vol. 2, 1819.
40. LAENNEC, R. T. H.: *Traité de l'Auscultation Mediate et des Maladies des Poumons et du Cœur*, 2nd ed., Paris, Claude, vol. 2, 1826.
41. LATHAM, P. M.: *Lectures on Subjects Connected With Clinical Medicine: Comprising Diseases of the Heart*, Philadelphia, Barrington & Haswell, 1847.
42. LAUBRY, CH.: Bull. et mém. de la Soc. méd. de hôp. de Paris, 3rd ser., 42, 327, 1918.
43. LENDON, G. A.: Med. J. Australia, 21, 613, 1934.
44. LEVINE, S. A.: *Clinical Heart Disease*, Philadelphia and London, Saunders, 1936.
45. LEVINE, S. A.: J. Am. Med. Assn., 101, 436, 1933.
46. LOCKWOOD, G. R.: *A Manual of the Practice of Medicine*, Philadelphia and London, Saunders, 1896.
47. LYON, D. M.: Edinburgh Med. J., N.S., 48, 589, 1941.
48. MACKENZIE, J.: *Diseases of the Heart*, London, Milford, 1908.
49. MARKSON, D. E., and GETNER, M. D.: Illinois Med. J., 82, 350, 1942.
50. McCRAE, T.: *Osler's Principles and Practice of Medicine*, 12th ed., New York and London, Appleton-Century, 1935.
51. MEYER, J.: Rev. de méd., 38, 35, 1921.
52. MONEY, A.: Medico-Chir. Trans., London, 65, 87, 1882.
53. NEUHOF, S.: *Clinical Cardiology*, New York, Macmillan, 1917.
54. NEUHOF, S.: *The Heart: Its Physiology, Pathology and Clinical Aspects*, Philadelphia, Blakiston, 1923.

55. NORRIS, G. W.: The Examination of the Circulatory System, in G. W. Norris and H. R. M. Landis' *Diseases of the Chest and the Principles of Physical Diagnosis*, 3rd ed., Philadelphia, Saunders, 1924.
56. OSLER, W.: *Trans. Assn. Am. Phys.*, 16, 2, 1901.
57. PENFOLD, W. J.: *J. Ment. Sci.*, 47, 87, 1901.
58. PITT, G. N.: *Guy's Hosp. Gaz.*, N.S., 19, 88, 1905.
59. PORTER: *The Post-Graduate*, 23, 537, 1908.
60. RUSSELL, W.: *Edinburgh Med. J.*, 28, Pt. 1, 130, 1882.
61. SANSOM, A. E.: *The Diagnosis of Diseases of the Heart and Thoracic Aorta*, London, Griffin, 1892.
62. SATTERTHWAITE, T. E.: *Diseases of the Heart and Aorta*, New York, Pelton, 1905.
63. SMITH, S. C.: *Heart Affections; Their Recognition and Treatment*, Philadelphia, Davis, 1920.
64. SOLIS-COHEN, M.: *AM. J. MED. SCI.*, 126, 131, 1903; *Trans. Lehigh Valley Med. Assn.*, Ser. 2, 1, 87, 1903.
65. SOLIS-COHEN, M.: *Penna. Med. J.*, 13, 216, 1909.
66. SOLIS-COHEN, M.: Personal observations since 1909.
67. SUTTON, H. G.: *Some Remarks on Tricuspid Regurgitant and Mitral Pre-systolic Bruits*, London, Churchill, 4, 288, 1867-8.
68. WHITE, P. D.: *Heart Disease*, New York, Macmillan, 1931.
69. WILSON, J. C.: *Medical Diagnosis in General*, in N. B. Potter and J. C. Wilson's *Internal Medicine*, 5th ed., Philadelphia and London, Lippincott, vol. 2, 1919.
70. WOLFERTH, C. C., and MARGOLIES, A.: *Med. Clin. North America*, 14, 897, 1931.
71. WOLFERTH, C. C., and MARGOLIES, A.: *New Internat. Clin.*, 1, 186, 1940.
72. WOOD, H. C., and FITZ, R. H.: *The Practice of Medicine*, Philadelphia, Lippincott, 1897.

## A HEREDOFAMILIAL NEUROLOGIC DISEASE, RESEMBLING CHARCOT-MARIE-TOOTH TYPE OF PROGRESSIVE MUSCULAR ATROPHY, IN A CHINESE FAMILY

. BY MAJOR CALVIN F. KAY, M.C.

AND

MAJOR HERBERT S. GASKILL, M.C.

20TH GENERAL HOSPITAL, A.P.O. 689, NEW YORK, N. Y.

ABOUT 100 years ago a bride of the family Ch'iu came to Pi-Shan, a village of Szechwan Province in western China. She bore the deformities and weaknesses of a disease which in the next 3 generations afflicted 11 of her 15 descendants who survived infancy. One of these, a Chinese soldier, was studied in a United States Army hospital. Our information concerning the family history and the general characteristics of the disease was supplemented by Dr. Chang Kuang-Hua of the Chinese National Health Administration, who visited and examined the mother and 4 siblings of our patient.

**Family History.** (See also a later paragraph.) In this predominantly male family (Fig. 1) there was only 1 normal male descendant out of 12 males born in 3 generations, but 2 of the 3 females were normal. The hereditary trait in this family had dominant characteristics without sex linkage, afflicting and transmitted by both sexes. The progeny of the 1 normal descendant who bore children were not diseased. The afflicted individuals could usually be distinguished from infancy by the presence of a flexion deformity of the hands. At about the age of 6 or 7 the children would stumble and fall when they ran. The weakness of the extremities was frequently accompanied by a sensation of numbness in the distal segments. Some of the individuals were moderately subnormal mentally, others were of average or above

average intelligence. In the males there was a high incidence of impotence. Characteristically the symptoms were worse in winter than in summer, and immediate subjective improvement occurred in going from a cold to a warm environment. The degree of incapacity varied considerably in different individuals, but those with even the mildest manifestations were clearly abnormal.

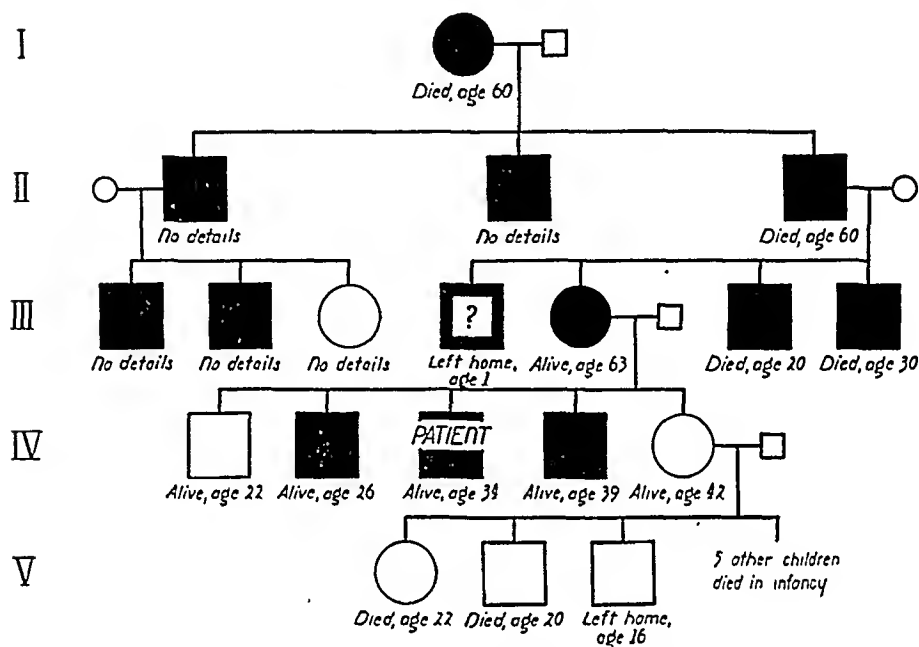


FIG. 1.—Descendants of the bride of the family Ch'iu. Males indicated by squares, females by circles. Afflicted individuals indicated by solid figures.

In most instances there was little if any progression of the disease after childhood. Occasionally, as in our patient, there was an irregular progression. Life expectancy did not appear to be greatly influenced; at least 3 of the afflicted individuals lived beyond the age of 60 years.

**Case History.** Our patient, Wu Fang Lin, aged 34 (Figs. 2 and 3), was recognized to be defective as an infant by the continuous flexion of his hands when at rest. From childhood he was weak and clumsy, unable to run properly or otherwise partake in strenuous games. He learned to read and write, and thereafter participated in the operation of his parents' small merchandise shop. At the age of 25, he was taken into the Army where he performed camp duties adequately but could neither run nor endure long marches. His superiors recognized his physical handicap, assigned him to light tasks, and finally, after 3 years of service, discharged him. He returned to his home and again devoted his time to buying and selling and such book work as was necessary in the shop. He was again called into the Army in October 1942, then aged 33. Although weakness prevented the performance of full duty, he was flown to India for training in February 1943. During the following 2 or 3 months his symptoms progressed rapidly. By May, when he was admitted to our hospital, he was able to walk only with the support of two canes. In addition to his weakness, he complained of numbness of his extremities and genitalia. He had not had a penile erection in many years. He had noted no sphincter disturbances.

Examination showed no significant abnormalities except those apparently related to his disease. He was of average size and intelligence. Except when attending to the necessities of life he remained practically motionless and expressionless, lying down or sitting propped up in bed.

Neurologic examination disclosed the following findings: The pupils were round and equal; they reacted to light and accommodation. The extra-ocular movements were full; there was no nystagmus; the corneal reflexes were active. The left palpebral fissure was narrower than the right, but this had more the appearance of an asymmetry than a true ptosis. The disks were well defined and of good color; there was a patch of medullated fibers on the temporal side of the left retinal fundus. The maculae and vessels were normal. There was no weakness of the muscles of the face, palate or tongue. Pain and tactile sensations were normal over the face.



FIG. 2.—Wu Fang Lin.

The hands were constantly held with the fingers flexed, but there were no contractures; the fingers could be passively extended with ease. The hand grips were very feeble; extension of the fingers and of the hands at the wrists was very weak. The strength of forearm movements was diminished, of shoulder movements well maintained. All movements of the toes and feet were extremely weak; there was moderate weakness of movements of the leg and thigh. With his arms folded across his chest he was unable to sit up from the recumbent position. There was moderate atrophy of the intrinsic musculature of the hands and feet, but elsewhere the muscular development was within normal limits. There was generalized hypotonia. Due to the weakness of the extremities no satisfactory evaluation of synergy or dys-

metria could be made. The patient was able to write Chinese characters crudely but legibly.

Biceps, triceps and patellar reflexes were active and equal, the Achilles reflexes were diminished. The abdominal and cremasteric reflexes were present. There were no pathologic reflexes. His gait was an indescribable combination of steppage, ataxia and general weakness, requiring the support of a cane in one hand and a fixed object in the other. In the Romberg position with the eyes closed the patient would fall.



FIG. 3.—The patient. Especially note the characteristic position of the hands.

There was hypesthesia to pin prick and loss of light touch in the distal segments of the extremities. Vibration was also lost in the extremities. Sense of position was uncertain in the big toes and thumbs.

Laboratory studies showed no abnormality. These included blood counts, urinalyses, blood Kahn, spinal fluid examination, nasal smears for leprosy, Roentgen rays of the entire spine, and biopsies from the deltoid and soleus muscles.

He was under observation in the hospital for a period of over 1 year during which time the only change observed was a slight increase in his muscular weakness. Prostigmine (0.001 gm. hypodermic) produced salivation and abdominal cramps without otherwise affecting his symptoms. Quinine sulfate (1.28 gm.) and potassium citrate (5 gm.) were likewise ineffective. General warming of the body produced subjective improvement without objective change.

The mother and 4 siblings of the patient were examined by Dr. Chang Kuang-Hua. The youngest brother, age 22, and the sister, age 43,



showed no signs of neurologic disease. The children of the sister were not examined, but were said to have been normal. The mother, age 63 years, had had numbness and weakness and a flexion deformity of her hands from early childhood. She had required a cane for support from the age of 40, but felt that her symptoms were little if any worse than in her childhood. The 2 afflicted brothers, aged 39 and 26 years, had similar symptoms. Neither had had a penile erection in many years. The mother was of above average intelligence, the afflicted brothers were mentally dull and had poor memories. All 3 had deformed hands, impaired sensations in the extremities and active deep reflexes throughout. None had apparent muscular atrophy or hypertrophy.

**Differential Diagnosis.** The following diseases were considered in differential diagnosis: myasthenia gravis, Friedreich's ataxia, progressive muscular dystrophy, spinal muscular atrophy and progressive muscular atrophy of the Charcot-Marie-Tooth type.

Myasthenia gravis was readily eliminated since activity had little effect in producing fatigue and rest did not result in improvement; this was substantiated by the absence of favorable response to prostigmine or unfavorable response to quinine. Although this disease bore a superficial similarity to Friedreich's ataxia in its hereditary nature, muscular weakness and sensory disturbances, the 4 cardinal signs, nystagmus, slurred speech, kyphoscoliosis and pes cavus, were missing. Progressive muscular dystrophy was eliminated from consideration by the distribution of the muscular weakness predominantly in the distal segments of the extremities, the presence of sensory abnormalities, and the absence of dystrophic changes in the muscle biopsies. The hereditary nature of this disease, its early appearance and benign course eliminated spinal muscular atrophy.

This hereditary neurologic disease appears to fit into the category of the Charcot-Marie-Tooth type of progressive muscular atrophy. The early onset of the disease together with its benign nature, the predominant occurrence in males, the involvement of the distal segments of the extremities and the heredofamilial characteristics of the illness all point to this diagnosis. Muscular weakness disproportionate to the degree of muscular atrophy is an atypical feature; however this syndrome seems to fit better into this category than any of the other known heredofamilial neurologic diseases.

**Summary.** A case of muscular weakness and atrophy together with sensory abnormalities which began in early childhood, occurring in a Chinese soldier has been described. A similar affliction was observed in his mother and 2 of his siblings. The disease is said to have occurred in 11 of 15 descendants of his maternal great-grandmother who suffered from the same disease. While this disease does not fit precisely into any of the known types of heredofamilial neurologic diseases, it most closely approximated the Charcot-Marie-Tooth or neural type of progressive muscular atrophy.

## A STUDY OF THE GOITROGEN, PROMIZOLE,\* WITH REFERENCE TO THE THYROID, METABOLISM AND THE BLOOD

BY GEORGE M. HIGGINS, PH.D.

ROCHESTER, MINN.

(From Division of Experimental Medicine, Mayo Foundation)

EXPERIMENTAL goiter has often been produced in animals that were fed diets in which suboptimal intakes of iodine were provided. Organic substances in vegetable sources also have proved to be goitrogenic. Leaves of plants and seeds of the Brassica family (cabbage, cauliflower and broccoli) were potent sources for such thyroid-stimulating factors.<sup>13,18,25,26</sup> Likewise soy bean flour contained a factor that proved goitrogenic.<sup>24</sup> Phenylthiocarbamide produced large hyperplastic goiters.<sup>23</sup> The thyroid hyperplasia induced by many of these agents, however, was prevented by the simultaneous administration of iodine. Amounts as low as 2  $\mu$ g. per day were adequate to prevent the thyroid hyperplasia in animals fed soy bean flour. Likewise, experimental goiters produced by methyl cyanide<sup>17</sup> or by potassium thiocyanate<sup>1</sup> were inhibited by the simultaneous administration of iodine.

Kennedy and Purves<sup>13</sup> in New Zealand, however, were unable to prevent the hyperplasia of the thyroid that ensued on feeding Brassica seeds, by giving iodine in amounts as high as 1000  $\mu$ g. per day, injected in the form of iodide. Thus the thyroid-stimulating effect of this factor, concentrated in the seeds of these plants, was unrelated to iodine deficiency. Subsequently Purves<sup>20</sup> showed that diiodotyrosine (1.7 mg. per day) only modified the extent of thyroid hyperplasia but that thyroxine (3 to 10  $\mu$ g. daily) completely inhibited these thyroid changes. The conclusion was indicated that some factor or factors in the seeds inhibited the synthesis of thyroxine, resulting in an increased output of thyrotropic hormone. Cytologic studies had previously shown that the pituitaries of rats fed the Brassica seed diet contained increased percentages of the basophilic cells with hyalinization and vacuolation and a simultaneously decreased percentage of the acidophilic cells.<sup>9</sup>

In this country MacKenzie and MacKenzie,<sup>15</sup> and Astwood, Sullivan, Bissell and Tyslowitz<sup>3</sup> showed that certain sulfonamide compounds and thiourea-like drugs were likewise goitrogenic and that their thyroid-stimulating potencies were not inhibited by the co-administration of iodine. Astwood<sup>1</sup> identified two chemical groups that depressed thyroid function. Those which contained the combination  $\text{NH}\cdot\text{CS}\cdot\text{NH}$  caused thyroid hyperplasia and those which contained an aniline group, as certain sulfonamide compounds, likewise were goitrogenic. Such goiters could be inhibited by thyroxine or desiccated thyroid but diiodotyrosine was without any effect.

Although both groups of goitrogens, namely, the iodine-inhibited goitrogens such as potassium thiocyanate and the iodine-resistant

\* Promizole (4,2'-diaminophenyl-5'-thiazolyl sulfone) was made available for this study through the courtesy of Drs. E. A. Sharp and L. A. Sweet of Parke, Davis & Co.

goitrogens such as thiouracil,<sup>21</sup> produced, when given to rats, extreme hyperplasia of the thyroid glands, yet there were marked differences in the capacities of the stimulated glands to take up iodine. Using tracer doses of radioactive iodine, Rawson, Tannheimer and Peacock<sup>22</sup> learned that the average uptake of iodine by the normal unstimulated gland was 56% of the administered dose. Thyroid glands made goitrous by potassium thiocyanate took up 87% while those stimulated by thiouracil took up 10% of the injected tracer dose of iodine.

The effect of these goitrogens, thiourea or thiouracil, it is agreed, is on the thyroid cells where a functional thyrostatics, inhibiting formation of thyroxine, has occurred. In the rat, the drug appears to interfere with the incorporation of iodine into diiodotyrosine and into thyroxine by the thyroid cell. Astwood and Bissell<sup>2</sup> have shown that thiouracil induced a nearly complete depletion of iodine from the thyroid gland, a result that was nullified by administration of thyroxine. The thyroid hyperplasia that ensued on giving the drug was the result of thyrotropic stimulation. But Astwood and Bissell<sup>2</sup> showed that the injection of large amounts of this pituitary hormone caused but a relatively small loss of thyroid iodine. Iodine concentrations in the thyroid gland proved to be a function of the amounts of thiouracil administered to the animal.

Basal oxygen consumption declined by 10% in 5 to 7 days and by 20% in 10 to 14 days in animals that were made goitrous by adding sulfaguanidine to their diet.<sup>16</sup> Prolonged feeding of the drug reduced the basal metabolic rate to thyroidectomy levels but its withdrawal from the diet resulted in a prompt return of the basal metabolic rates to normal levels.

In addition to certain sulfonamide compounds and thiourea-like derivatives the sulfone, promizole (4,2'-diaminophenyl-5'-thiazolyl sulfone) has been shown to be goitrogenic.<sup>11</sup> Feldman, Hinshaw and Mann<sup>6</sup> learned that this sulfone exerts a very favorable influence on the course of experimental tuberculosis in guinea pigs. The changes exerted by the drug on the thyroid gland are not unlike those induced by the previously described goitrogens and include increases in the acinar cell heights, in the number of thyroid acini and in the total gland weights and destruction and final disappearance of the colloid bodies from the thyroid acini.

This report is a summary of additional studies of the effects of promizole on the thyroid and pituitary glands, on consumption of oxygen and on the formed elements of the blood.

**Method.** Immature rats weighing from 60 to 80 gm. have been used. Purified diets were provided in small ointment cups with covers so adapted as to restrict waste of food. The diet was as follows: sucrose, 74%; purified vitamin-free casein, 20%; corn oil (Mazola), 4%; Osborne-Mendel salt mixture, 2%. Cod-liver oil was provided by mouth weekly and 1 cc.\* of a mixture of the vitamin B fractions was given daily by catheter. On this diet our control rats grew satisfactorily and their growth curves were normal.

\* Each cc. contained 100  $\mu$ g. of thiamine, 200  $\mu$ g. of riboflavin, 100  $\mu$ g. of pyridoxine, 200  $\mu$ g. of pantothenate, 1 mg. of niacin and 10 mg. of choline chloride. These vitamins were courteously provided me by Merck & Co., Rahway, N. J.

Promizole was administered in various ways. Suspensions in distilled water have been given daily by mouth or by the intraperitoneal route. Varying amounts have been given, ranging from 5 to 25 mg. per rat per day. When thyroxin, desiccated thyroid or sodium iodide was given concomitantly with the drug, it was provided as follows: thyroxin, 50  $\mu$ g. daily, intraperitoneally; desiccated thyroid, 0.25% in the diet; sodium iodide, intraperitoneally, so that each rat received 100  $\mu$ g. of iodine daily.

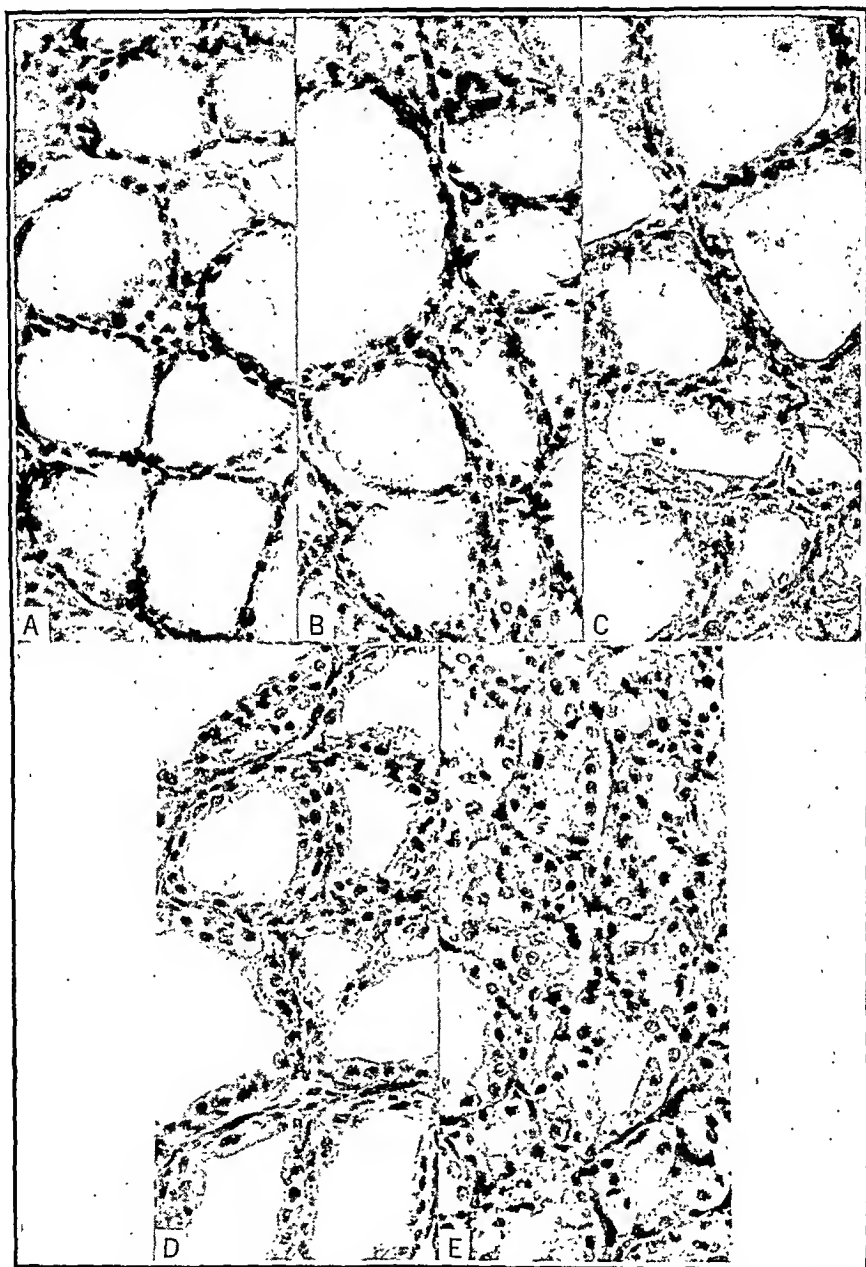


FIG. 1.—Sections of thyroid glands of young rats that received 25 mg. of promizole daily. A, Control thyroid. B, Thyroid gland after 2 daily injections. C, Thyroid gland after 3 daily injections. D, Thyroid gland after 7 daily injections. E, Thyroid gland after 10 daily injections.

Data on oxygen consumption were obtained by means of a closed circuit apparatus attached to a Krogh spirometer.<sup>5</sup> Three successive readings were taken on animals following a 16 to 20 hour fast and the number of calories per square meter per hour was computed. The formula of Lee (S.A. =  $12.54 \times W^{0.60}$ )<sup>14</sup> was used to compute the surface area from the body weight.

Animals were weighed at intervals on a dietitian's scale. At necropsy the thyroid glands were quickly dissected from the trachea, freed of connective tissue, weighed on a precision balance to 0.1 mg., fixed in formalin and prepared for histologic study. Likewise the pituitaries were removed and weighed and in some instances histologic sections were prepared.

Hematologic determinations were made on heparinized samples of blood withdrawn from the heart. The total number of erythrocytes and the total number of leukocytes per c.mm. of blood were determined. The grams of hemoglobin per 100 cc. of blood, the size of the red cells in cubic microns and the differential leukocyte distributions were determined, using standard techniques.

In many instances promizole concentrations in the blood were obtained on samples taken by cardiac puncture. Determinations were made, using the modified Marshall technique,<sup>4</sup> employing the Sheard-Sanford photometer for colorimetry.

**Results. I. The Effect of Giving 25 Mg. of Promizole Daily, Intraperitoneally, to Young Male Rats for 10 Days.** The weights of the animals and of their thyroid gland and pituitary gland are shown in Table 1. The histologic appearance of the thyroid glands is shown in Figure 1. All animals failed to gain in weight after the 3rd day. There were some anorexia and considerable alopecia. Increases in the weights of the thyroid glands were not significant until the 3rd day but by the 10th day the glands had approximately doubled in size. No significant changes were observed in the absolute or relative weights of the pituitaries during the 10 day period (Table 1). The initial effect on the histologic structure of the thyroid involved changes in the colloid bodies (Fig. 1). On the 3rd day, colloid bodies were fragmented and significant increases were observed in cell heights. By the 7th day colloid bodies had essentially disappeared and on the 10th day extensive hyperplasia of the thyroid cells had practically obliterated the lumina of the thyroid follicles (Fig. 1).

TABLE 1.—EFFECTS OF GIVING PROMIZOLE (25 MG. DAILY, INTRAPERITONEALLY) FOR 10 DAYS ON THE WEIGHTS OF THE THYROID AND PITUITARY GLANDS

Injections	Elapsed time (hrs.)	Attained body weight (gm.)	Thyroid gland (mg.)		Pituitary gland (mg.)	
			Absolute	Per 100 gm. body weight	Absolute	Per 100 gm. body weight
0 . . . . .	0	72	6.5	8.9	3.3	4.5
2 . . . . .	48	75	6.9	9.2	3.1	4.2
3 . . . . .	72	82	9.6	11.8	3.1	3.9
7 . . . . .	168	74	11.3	15.6	2.5	3.9
10 . . . . .	240	61	12.8	20.9	2.6	4.2
0 . . . . .	240	104	7.9	7.6	3.3	3.1

**II. The Effects of Giving Thyroxin, Desiccated Thyroid and Sodium Iodide, While Giving Promizole (25 Mg.) Daily for 14 Days.** Sixty young rats having an average weight of 62 gm. were placed on the purified diet. Forty of these received 25 mg. of promizole by mouth daily, 10 received the same amount intraperitoneally and 10 were given water without promizole and served as controls. Of the 40 animals

that received promizole by mouth, 10 animals received in addition 50  $\mu$ g. of thyroxin daily, 10 animals received desiccated thyroid at a 0.025% level in their diet, 10 animals received sodium iodide in an amount equivalent to 100  $\mu$ g. of iodine daily and 10 animals received promizole alone. Observations continued for 14 days.

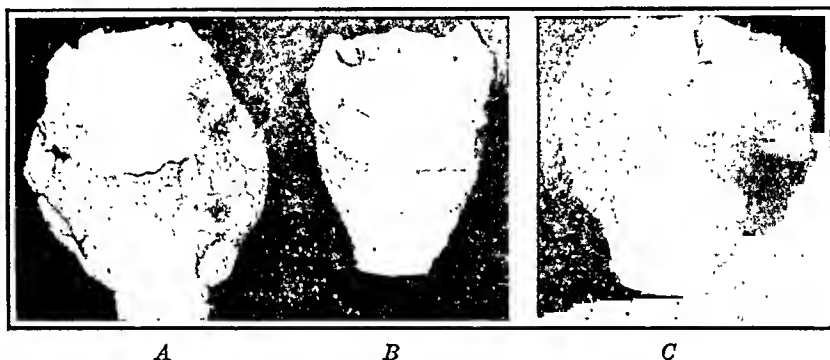


FIG. 2.—Gross appearance of thyroid glands of animals that received 14 daily injections of promizole. A, Promizole alone. B, Promizole when co-administered with thyroxin. C, Promizole when co-administered with sodium iodide.

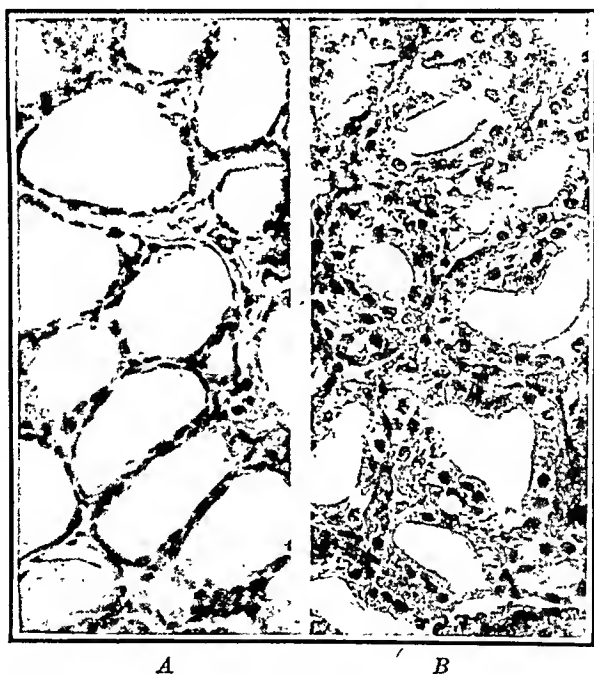


FIG. 3.—Histologic appearance of thyroid glands of animals that received 14 daily injections of promizole. A, Promizole plus thyroxin. B, Promizole plus sodium iodide.

The gross appearance of the thyroid glands of animals that received the goitrogen alone, and of those of animals that received thyroxin or sodium iodide, together with the goitrogen, is illustrated in Figure 2. The differences in the cytologic appearance of the thyroids of animals

that received thyroxin with the goitrogen and those that received sodium iodide with the goitrogen are shown in Figure 3.

The data assembled on the body weights of these animals and the weights of their thyroid glands and their pituitary glands, together with their probable errors, are included in Table 2. It is obvious from the data that the co-administration of either thyroxin or desiccated thyroid completely inhibited the goitrogenic action of promizole. Fifty  $\mu$ g. of thyroxin was, of course, greatly in excess of the daily requirement of a rat but attempts were not made to determine the minimal amounts necessary to inhibit the goitrogenic action of promizole. The addition of sodium iodide at such a level that 100  $\mu$ g. of iodine was given daily proved ineffective in restricting the goitrogenic action. In fact, both the absolute weights and the relative weights of the thyroid glands of these animals that received iodine were significantly greater than those obtained when animals were given promizole alone (Table 2).

TABLE 2.—EFFECTS OF GIVING PROMIZOLE (25 MG. DAILY) FOR 14 DAYS AND THE INFLUENCE ON THE THYROID AND PITUITARY GLANDS OF GIVING THYROXIN, DESICCATED THYROID OR SODIUM IODIDE AT THE SAME TIME

Route of administration of promizole	Supplemental therapy	Animals	Attained body weight (gm.)	Thyroid gland (mg.)		Pituitary gland (mg.)	
				Absolute	Per 100 gm. body weight	Absolute	Per 100 gm. body weight
0	0	10	85	13.6 $\pm$ 0.7*	16.8 $\pm$ 1.2	3.3 $\pm$ 0.2	3.9 $\pm$ 0.2
Oral	0	10	99	30.1 $\pm$ 3.9	29.6 $\pm$ 3.9	4.8 $\pm$ 0.3	4.8 $\pm$ 0.2
Intraperitoneal	0	10	104	42.4 $\pm$ 2.6	40.2 $\pm$ 1.9	5.4 $\pm$ 0.2	5.2 $\pm$ 0.2
Oral	†	10	77	10.4 $\pm$ 0.7	13.3 $\pm$ 0.7	3.7 $\pm$ 0.1	4.8 $\pm$ 0.2
Oral	‡	10	62	8.8 $\pm$ 0.5	14.1 $\pm$ 0.9	3.1 $\pm$ 0.1	4.9 $\pm$ 0.2
Oral	§	10	98	48.8 $\pm$ 3.3	50.5 $\pm$ 4.0	4.7 $\pm$ 0.2	4.8 $\pm$ 0.2

\* Figures following each  $\pm$  sign are probable errors of the mean.

† Thyroxin, 50  $\mu$ g. daily, intraperitoneally.

‡ Desiccated thyroid, 0.025% in the diet.

§ Sodium iodide, 100  $\mu$ g. of iodine daily as sodium iodide, subcutaneously.

These thyroid changes were accompanied in this series of animals by increases in the weights of the pituitary glands of all animals that received the goitrogen alone and those that received the goitrogen plus iodine. But the weights of the pituitaries recorded for animals that received thyroxin or desiccated thyroid together with the goitrogen were no greater than in untreated controls. However, because of the loss of body weight of all animals receiving thyroid hormone the ratios of the weights of their pituitaries to their body weights were considerably greater than those of the untreated controls. Thus the co-administration of iodine, which did not restrict the thyroid hyperplasia, likewise did not restrict the increases of pituitary weight observed when animals received the goitrogen alone (Table 2).

III. *The Influence of Sex on the Thyroid and Pituitary Changes That Were Induced by Giving Promizole, 25 Mg. Daily, to Adult Rats.* Although immature rats are known to be more susceptible to the action of goitrogens than adults, a study was made of the influence of the sex factor on the changes induced by promizole in adult rats. For this study our standard laboratory rat ration was provided *ad libitum*. A group of 16 males weighing an average of 165.8 gm. and a group of

16 females weighing an average of 130.4 gm. were selected. Half of each group were given 25 mg. of promizole, in a water suspension, by mouth daily and the other half served as a control group. Observations were continued for 3 months.

The data on the body weights of these animals and on the absolute weights and relative weights per 100 gm. of body weight of their thyroid and pituitary glands are condensed into Table 3. It is obvious that the goitrogen had no significant effect on the further growth of these adult rats during the 3 month test period. In each sex, the average attained body weight of the test group of animals was less than that of its control group; yet the differences were not statistically significant. The reactions of the thyroid gland to the goitrogen, however, were much greater in the females than in the males, attaining, in the former sex an average thyroid gland weight that was nearly twice that which developed in the males. Sex differences in the increases in the weights of the pituitary glands were likewise observed. In the males, the mean pituitary gland weight of the test group was  $1.2 \pm 0.4$  mg. greater than that of the control group; this is perhaps a barely significant increase. But in the female group of rats this same difference was  $2.4 \pm 0.6$  mg. and indicates that the pituitaries of the test females were significantly larger than those of control females. This increase in the size of the pituitary may bear some relationship to increased hyperplasia of the thyroid glands in test females.

TABLE 3.—EFFECTS OF GIVING PROMIZOLE (25 MG. DAILY, BY MOUTH) TO ADULT MALE AND FEMALE RATS FOR 3 MONTHS

Sex	Promizole administered daily (mg.)	Attained body weight (gm.)	Thyroid gland (mg.)		Pituitary gland (mg.)	
			Absolute	Per 100 gm. body weight	Absolute	Per 100 gm. body weight
Male . . .	0	233.0 $\pm$ 8.1*	12.4 $\pm$ 0.7	5.4 $\pm$ 0.3	6.1 $\pm$ 0.1	2.6 $\pm$ 0.2
Male . . .	25	203.5 $\pm$ 9.8	32.1 $\pm$ 3.1	16.7 $\pm$ 2.2	7.3 $\pm$ 0.4	3.8 $\pm$ 0.3
Female . . .	0	153.4 $\pm$ 4.1	11.3 $\pm$ 0.3	7.4 $\pm$ 0.3	7.0 $\pm$ 0.2	4.6 $\pm$ 0.2
Female . . .	25	145.7 $\pm$ 5.1	61.2 $\pm$ 5.7	41.8 $\pm$ 3.3	9.4 $\pm$ 0.6	6.4 $\pm$ 0.3

\* Figures following each  $\pm$  sign are probable errors of the mean.

All test animals, males and females, received by mouth the same amounts of the goitrogen each day. But since the mean body weight of the animals constituting the female test group was less, by 57.8 gm., than that of the male test group, the increased weights of the thyroid gland and pituitary gland found in females may be due to greater drug concentrations in the blood. In the females, the average concentration of the goitrogen at the end of the experiment was 1.03 mg. per 100 cc. of blood while in the males it was 0.33 mg. per 100 cc. That there may be a real sex difference is indicated by the work of Mixner, Reineke and Turner,<sup>19</sup> who reported that female chicks exhibited a greater thyroid response to thiouracil than males and that females required greater amounts of thyroxin to depress thyroid weights or to maintain them at normal levels than males.

Although promizole exerts certain toxic and untoward influences on the hemopoietic system of growing rats, significant differences were not observed between the data assembled on the formed elements of the



blood of animals constituting the test and control groups. These data are not presented in tabular form but are included for comparison. Among the females, the control group had a mean erythrocyte level of 9,090,000 cells per c.mm. of blood, a hemoglobin level of 14.3 gm. per 100 cc. of blood and 10,950 leukocytes per c.mm. of blood. The data for the test group were respectively 9,000,000 red blood cells, 13.5 gm. of hemoglobin and 13,050 leukocytes. Among the males, the corresponding data of the control group were as follows: 8,950,000 red blood cells, 15.9 gm. of hemoglobin and 16,050 leukocytes. The data on the test group were 8,660,000 red blood cells, 13.2 gm. of hemoglobin and 13,150 leukocytes. It was obvious that neither anemia nor leukopenia had occurred. Alopecia, common among immature rats when this goitrogen is fed to them, did not occur in adults.

IV. *The Effect on the Formed Elements of the Blood of Growing Rats, of Giving Promizole, 25 Mg. Daily, for 10 Weeks.* Twenty-five young male rats, having an average body weight of 54.4 gm., were selected. The high carbohydrate purified ration was provided *ad libitum*. Promizole, 25 mg. suspended in water, was given orally, each day except Sunday, to 15 of the 25 rats for the following 10 weeks. The remaining 10 rats received an equivalent amount of water each day; these served as controls.

The data assembled from blood samples obtained by cardiac puncture at the end of the 10th week have been condensed into Table 4. It is obvious that in the growing rat fed a purified diet, entirely suitable for normal growth and hemopoiesis, anemia developed when the animal was given promizole at a level of 25 mg. daily. There were no changes observed in the total number of leukocytes. Although clinically, granulocytopenia had been observed, the differential percentage distribution recorded for this series of rats showed a marked increase in the relative number of granulocytes. This, it would seem, is probably correlated with a hemopoietic response to the tissue damage which was exerted by the drug.

TABLE 4.—THE EFFECTS ON THE FORMED ELEMENTS OF THE BLOOD OF GIVING PROMIZOLE (25 MG. DAILY, BY MOUTH) FOR 10 WEEKS

	Control	Test
Animals . . . . .	10	15
Promizole daily, mg. . . . .	0	25
Erythrocytes:		
Millions per c.mm. . . . .	9.6 $\pm$ 0.3*	6.9 $\pm$ 0.2
Size in $\mu$ . . . . .	42.1 $\pm$ 0.5	49.8 $\pm$ 0.8
Hemoglobin, gm. per 100 cc. . . . .	15.9 $\pm$ 0.5	12.1 $\pm$ 0.2
Leukocytes, thousands per c.mm. . . . .	16.2 $\pm$ 1.0	18.8 $\pm$ 1.4
Reticulocytes, % of erythrocytes . . . . .	3.9 $\pm$ 0.7	14.8 $\pm$ 2.2
Lymphocytes . . . . .	85.5 $\pm$ 1.6	71.0 $\pm$ 1.9
Monocytes . . . . .	1.0	1.1
Granulocytes:		
Neutrophilic . . . . .	12.0 $\pm$ 1.4	26.7 $\pm$ 1.9
Eosinophilic . . . . .	0.8	0.5
Basophilic . . . . .	0.7	0.7

\* Figures following each  $\pm$  sign are probable errors of the mean.

V. *The Effects of Giving Graded Amounts of Promizole, 5, 10 and 15 Mg. Daily, Intraperitoneally, for 6 Weeks to Young Growing Rats.*

Forty young male rats, weighing between 80 and 90 gm., were selected. They were fed the purified high carbohydrate diet and each received the vitamin fractions in amounts previously stated. Ten of these received 5 mg. of promizole intraperitoneally daily in 1 cc. of distilled water, 10 received 10 mg. daily, 10 received 15 mg. daily and 10 received an equivalent amount of distilled water. The latter group of 10 rats constituted the control group. Observations were continued for 6 weeks. Water intake per rat per day was measured during the 3rd week of the test. The amount of food consumed was measured each day, during the 2nd, 3rd, 4th and 5th week. The oxygen consumption was recorded for each rat in these groups at the end of each week of the experiment. Heart blood was sampled at the end of the 6th week and the various determinations were made. At necropsy the weights of the thyroid and the pituitary glands were obtained and values proportional to their body weight were established.

(a) *Water Intake.* Animals receiving 15 mg. of the goitrogen daily took the largest amounts of water. The average daily intake per rat during the week in which measurements were made was 18.5 cc. for the control group, 20.2 cc. for those receiving 5 mg. daily, 19.3 cc. for those receiving 10 mg. daily and 32.9 cc. for those receiving 15 mg. daily.

(b) *Food Intake and Body Weight.* Varying the amounts of the goitrogen given daily had considerable influence on the volume of food taken each day. During the 4 weeks, when daily measurements of food consumed were recorded, each control animal consumed from 12 to 16 gm. of food daily. The average intake per rat per day of those receiving 5 mg. was 14.4 gm., of those receiving 10 mg. the intake was 10.8 gm., and of those receiving 15 mg. the intake was 10.5 gm. of food per day. Thus the drug exerted some influence on appetite, which was reflected in the attained weights of these animals. During the test period (6 weeks) the average gain per control rat was 120 gm. or 20 gm. per week. The average weekly gains in body weight recorded for the 3 test groups, receiving 5, 10 and 15 mg. of promizole daily were respectively 17.2 gm., 11.3 gm. and 7.5 gm. Although the food intake per rat per day of those receiving 15 mg. was essentially as much as that of those receiving 10 mg. of the drug, yet the increase in body weights of the animals in that group was significantly less. The drug may, in some way, restrict the action of enzymes in the gastro-intestinal tract so as to inhibit absorption and adequate utilization of the food consumed.

(c) *The Formed Elements of the Blood.* The blood data were condensed into Table 5. The administration of 5 mg. per day for 6 weeks did not significantly alter either the mean total erythrocyte count or the mean hemoglobin level, although the trend was down. Ten or 15 mg. of promizole per day proved more toxic, so that significant reductions in these categories were obtained in these groups. The total leukocyte tabulations were lowered and yet not significantly so except in Group II, receiving 10 mg. per day. Obviously leukopenia had not been produced. The data on the percentage distribution of

the white cells (Table 5) indicate, too, that granulocytopenia did not occur. On the contrary, the percentages of granulocytes found in the blood of all 3 test groups were significantly higher than in the control: a result, it would seem, probably due as before to the toxic influences which the drug had exerted on the tissues.

TABLE 5.—THE EFFECT ON THE FORMED ELEMENTS OF THE BLOOD OF GIVING GRADED DOSES OF PROMIZOLE (5, 10 AND 15 MG. DAILY) INTRAPERITONEALLY FOR 6 WEEKS

	Group			
	Control	Test I	Test II	Test III
Animals . . . . .	10	10	10	10
Promizole daily, mg. . . . .	0	5	10	15
Erythrocytes:				
Millions per c.mm. . . . .	8.0±0.2*	7.1±0.8	6.7±0.1	6.0±0.1
Size in $\mu$ . . . . .	48.8±1.0	52.7±1.2	47.5±0.9	50.0±0.2
Hemoglobin, gm. per 100 cc. blood	12.8±0.2	11.7±0.5	10.0±0.4	9.0±0.4
Leukocytes, thousands per c.mm.	15.4±0.7	12.7±1.0	9.1±0.9	12.8±0.8
Lymphocytes . . . . .	81.9±0.9	69.6±2.8	57.9±4.3	60.5±2.5
Monocytes . . . . .	0.7	1.4	1.0	2.5
Granulocytes:				
Neutrophilic . . . . .	15.4±0.9	28.3±0.3	41.1±4.4	37.0±2.7
Eosinophilic . . . . .	1.9	0.3	0	0
Basophilic . . . . .	0.1	0.4	0	0

\* Figures succeeding the  $\pm$  sign are probable errors of the mean.

(d) *The Weights of the Thyroid and Pituitary Glands.* Data on the absolute weights and weights per 100 gm. of body weight of the thyroid and pituitary glands have been condensed into Table 6. It seems obvious that the proportional increase in the daily administration of promizole induced somewhat proportional increases in the mean of the absolute weights of the thyroid glands. This fact is reflected, too, in the increases in their relative weights.

TABLE 6.—THE EFFECT ON THE THYROID GLAND AND PITUITARY GLAND WEIGHTS OF GIVING GRADED DOSES OF PROMIZOLE (5, 10 AND 15 MG. DAILY) INTRAPERITONEALLY FOR 6 WEEKS

Group	Animals	Promizole daily (mg.)	Thyroid gland (mg.)		Pituitary gland (mg.)	
			Absolute	Per 100 gm. body weight	Absolute	Per 100 gm. body weight
Control . . . . .	10	0	10.2±0.6*	6.1±0.3	6.9±0.3	4.2±0.6
Test I . . . . .	10	5	16.9±0.2	8.5±0.4	8.1±0.2	4.1±0.2
Test II . . . . .	10	10	38.2±0.3	24.5±1.8	8.9±0.3	5.7±0.2
Test III . . . . .	10	15	54.0±0.4	38.1±2.0	8.3±0.8	7.0±0.2

\* Figures succeeding each  $\pm$  sign are probable errors of the mean.

The pituitary glands of the test animals were all larger than those of the controls and yet there were no significant differences between the average weights of these glands of the 3 test groups. In other words, increasing the amounts of the drug, which did significantly increase the weights of the thyroid gland, did not further increase the weights of the pituitary glands.

Sections of the thyroid glands of these groups of animals are shown in Figure 4. There were a progressive increase in the heights of the acinar cells and a progressive destruction of the colloid bodies in the

thyroid glands of these animals as the amounts of the goitrogen were increased.

(e) *Concentration of Promizole in the Blood Stream of Animals Receiving 5, 10 and 15 Mg. Daily for 6 Weeks.* The following data on the concentration of the goitrogen in the blood stream were obtained from samples of heart blood withdrawn 24 hours after the drug was last administered. Determining the concentration at that time, that is, just before an ensuing administration, gave the probable minimal concentration in the blood. Data thus obtained indicated that 24 hours after the third daily administration there was a promizole concentration of 1.2 mg. per 100 cc. of blood in animals receiving 5 mg. of the drug daily, 1.7 mg. per 100 cc. in those receiving 10 mg. and 2.9 mg. per 100 cc. in the blood of those animals receiving 15 mg. daily; 24 hours

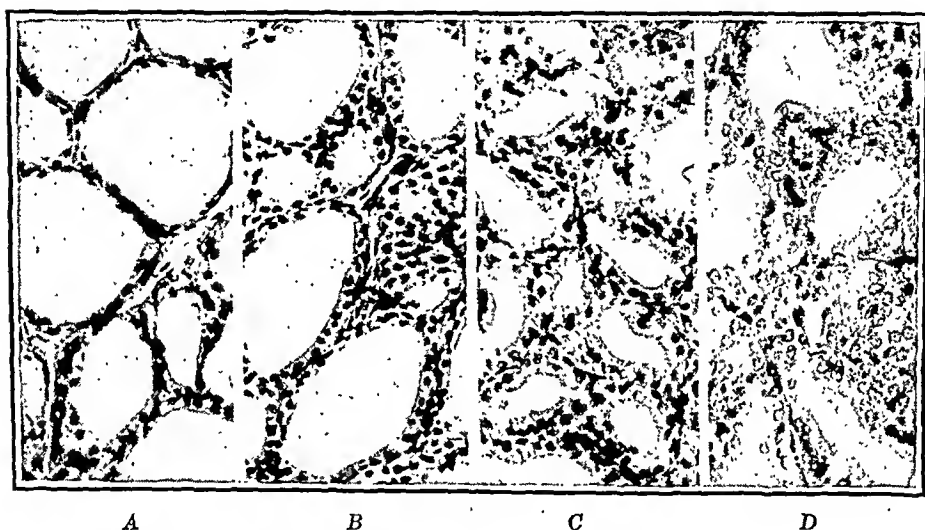


FIG. 4.—Histologic appearance of thyroid glands of animals that received promizole for 6 weeks. A, Thyroid of a control animal. B, Thyroid of an animal that received 5 mg. daily. C, Thyroid of an animal that received 10 mg. daily. D, Thyroid of an animal that received 15 mg. daily.

after the tenth daily administration of promizole, the blood concentrations of the respective groups were 1.7, 2.2 and 3 mg. per 100 cc. Twenty-four hours after the 14th day the concentrations were 1, 1.4 and 2.3 mg. per 100 cc. respectively. After the 21st day, they were respectively 0.8, 1.1 and 1.4 mg. per 100 cc. After the 10th day the blood concentrations were progressively less, in spite of the fact that the daily administration of the goitrogen was constant in amount within each group.

In a second series of 36 animals an attempt was made to determine the rapidity of absorption of promizole and the rate of its elimination from the body. Twelve young rats were given, by mouth, 5 mg., 12 were given 10 mg. and 12 were given 15 mg. One hour later the concentrations of the goitrogen in the blood were as follows: in animals receiving 5 mg., 1.6 mg. per 100 cc.; in those receiving 10 mg., 2 mg.

per 100 cc.; and in those receiving 15 mg., 3.3 mg. per 100 cc. At 3 hours after giving the drug, the respective concentrations were 1.8, 1.1 and 3.4 mg. per 100 cc., and at 6 hours, the respective concentrations were 0.3, 0.3 and 0.5 mg. per 100 cc. Barely a trace of the goitrogen was present in the blood of all 3 groups of animals 24 hours after the drug had been given a single time.

(f) *The Basal Metabolic Rates, Expressed in Calories per Square Meter per Hour, of Animals Receiving Graded Amounts of Promizole Daily.* Using the method previously described,<sup>5</sup> the oxygen consumption of these rats, receiving graded doses of promizole, was computed at the end of the 1st, 2nd, 3rd, 4th and 6th weeks. The data are condensed into Table 7. Calories per square meter per hour in the group of rats that did not receive the goitrogen were relatively constant during the entire 6 weeks period of the test. Basal metabolic rates of rats receiving 5 mg. of the goitrogen had dropped to -10.8% at the end of the 6 weeks period, the rates of those receiving 10 mg. had dropped to -23.5% and the rates of those receiving 15 mg. had dropped to -25.4%. Even within the 1st week of the administration of promizole these respective rates had dropped to -6.8, -7.2 and -14.5%, respectively. This prompt depression of the basal metabolic rates of rats fed promizole is in keeping with the experimental results obtained when sulfaguanidine was fed to rats<sup>16</sup> and with clinical observations as well.<sup>1</sup> Although our data on the consumption of oxygen by rats made goitrous by promizole clearly indicate reductions of the basal metabolic rates, yet there was extreme variability. Animals with extreme hyperplasia of the thyroid gland had rates well within the normal range. It may be that promizole does not completely block the synthesis of thyroxine. Whitehead<sup>27</sup> showed that the oxygen consumption of rats that were fed the goitrogenic Brassica seed diet and had extremely hyperplastic goiters was well within the limits accepted for normal for animals of the same weight and sex.

TABLE 7.—CALORIES PER SQUARE METER PER HOUR CONSUMED BY RATS RECEIVING GRADED DAILY AMOUNTS OF PROMIZOLE FOR 6 WEEKS

Promizole daily (mg.)	1 week	2 weeks	3 weeks	4 weeks	6 weeks
0 . . .	55.9±1.2*	55.2±2.2	50.5±0.9	59.2±1.2	57.4±1.6
5 . . .	52.1±1.7	50.3±2.9	48.6±2.2	49.1±2.5	50.5±1.4
10 . . .	51.7±1.4	38.8±1.4	48.9±1.2	45.9±1.4	43.9±1.4
15 . . .	47.8±1.5	42.0±0.9	42.3±1.7	42.9±1.5	42.8±1.6

\* Figures succeeding the ± sign are probable errors of the mean.

**Comment.** Promizole (4,2'-diaminophenyl-5'-thiazolyl)sulfone) caused thyroid hyperplasia in rats and may be considered a goitrogen, comparable in its thyroid-stimulating effects to thiourea, thiouracil or sulfaguanidine. As in the cases of goiters produced by the thiourea derivatives or sulfonamide compounds, goiters produced by promizole were not inhibited by iodine but were inhibited by the co-administration of either thyroxine or desiccated thyroid. Thus promizole may be considered as a thyroid inhibitor which in some way nullified the synthesis of thyroxine by the thyroid cell.

The effect on the thyroid gland of these thyroid-inhibiting goitrogens is apparently mediated through the pituitary. When animals had been previously hypophysectomized goiters did not develop when thiouracil or sulfaguanidine was given and comparable results were obtained when promizole was given to such animals.<sup>12</sup> The stimulation of the thyroid is apparently due to an increase in the output of thyrotropic hormone by the pituitary. MacKenzie and MacKenzie<sup>15</sup> have described the increases in the relative proportions of basophilic cells in the pituitary glands of animals made goitrous by sulfaguanidine. My colleagues and I have observed definite increases in the weights of most of the pituitary glands of animals made goitrous by giving promizole. This weight response, however, is by no means constant and these weight increases did not appear to correlate with the increase in the weights of the thyroids. In the few sections of the anterior lobes that we have studied, the proportions of the large, vacuolated, basophilic cells, the so-called thyroidectomy cells, were apparently increased. Actual cell counts were not made. Increasing the daily intake of promizole produced larger goiters but the absolute weights of the pituitary glands in animals receiving 15 mg. daily were no greater than in those which had received 5 mg. daily. There appeared to be an increase after 14 days in the weights of the pituitaries when 25 mg. of promizole was given but this may or may not be correlated with hyperplasia or hypertrophy of the basophilic cells in the anterior lobe. Williams, Weinglass, Bissell and Peters<sup>28</sup> reported that the pituitary glands of animals receiving thiouracil were smaller than normal. They could not detect any changes in the microscopic structure of these glands, such as has been described, and such as occurs after thyroidectomy.

Using the rate of metamorphosis of *Rana pipiens* larvæ as a test for the presence of thyrotropin in the pituitary gland and blood serum of rats made goitrous by thiourea, Gordon, Goldsmith and Charipper<sup>8</sup> concluded that the amounts of thyrotropic hormone in the gland and in the serum were less in test animals than in controls. They expressed the belief that the release of thyrotropic hormone from the pituitary into the blood stream is greater in test animals than in controls but that the hormone is more rapidly picked up and utilized by the enlarging goiter. On the other hand, using the thyroid glands of guinea pigs as test objects, Griesbach and Purves<sup>10</sup> showed that the serum of rats having greatly hyperplastic thyroid glands was significantly enriched in thyrotropic activity when compared with serum of control rats. The thyrotropic content of the pituitary was depleted but the percentage of basophilic cells was increased. The changes observed by Griesbach and Purves as a result of feeding a rapeseed diet are an increase of thyrotropin in the serum, a decrease of pituitary thyrotropin, an increase of the number and activity of the basophilic cells and a degranulation of the acidophilic cells.

The effect of these goitrogens on the thyroid gland is presumably due to restrictions in the utilization of iodine and in the consequent synthesis of thyroxine. The use of radioactive iodine has afforded reliable means for study of the changes that such goitrogens exert on

thyroid physiology. Rawson, Tannheimer and Peacock<sup>22</sup> showed that goiters induced by potassium thiocyanate took up 87% of tracer doses of radioactive iodine, while those induced by thiouracil took up but 10%. This was true in spite of the fact that the thyroids in thiouracil-treated rats were even more hyperplastic than those in the thiocyanate-treated animals. Franklin, Lerner and Chaikoff<sup>7</sup> showed that the thiouracil-stimulated thyroids were unable to concentrate radioactive iodine to the extent of the normal glands and that the amounts of iodine converted into thyroxine and diiodotyrosine were depressed in stimulated glands. But after administration of the drug had been stopped, normal concentrations of iodine were obtained in the thyroids in 2 weeks. Astwood and Bissell<sup>2</sup> showed that iodine practically disappeared from the thyroid glands when thiouracil was given to young rats but within 8 days after administration of the drug had been stopped there were a rapid accumulation of iodine and a prompt decrease of the size of the thyroid glands. They showed, too, that graded doses of thiouracil resulted in proportional increases of the weight of the thyroid gland and of the thyroid iodine concentrations and that the iodine concentrations in the thyroid were more delicate indications of reactions to thiouracil than the weights of the glands. Our own studies on the capacity of the promizole-stimulated thyroid gland to take up radioactive iodine are still incomplete. These data will be presented in a subsequent report.

The depression of the basal metabolic rates that my colleagues and I have ordinarily obtained in most of our animals given promizole confirms the observations hitherto reported on animals made goitrous by either sulfaguanidine or thiouracil. This fall of oxygen consumption leads us to conclude that promizole in some way may interfere with formation of thyroxine. Whereas the administration of thyroxine will inhibit the fall of metabolic rate, yet there is now no evidence to prove that the synthesis of thyroxine is completely inhibited by the promizole-stimulated thyroid. The results of our studies on oxygen consumption were often variable. Animals with extreme hyperplasia of the thyroid gland have been found to have basal metabolic rates that are well within the normal range. In these instances one is led to postulate the conclusion either that some thyroxine is being released by the promizole-stimulated thyroid or that there may be sites other than the thyroid for the synthesis of the thyroid hormone. Whitehead<sup>27</sup> was unable to demonstrate any depression of the basal metabolic rates of animals made goitrous by the rapeseed diet and he concluded that the hypertrophied thyroid still secreted enough hormone for the needs of the body.

**Conclusions.** 1. The administration of promizole to young rats results in changes in the thyroid glands that resemble those induced by thiourea-like compounds and certain sulfonamide compounds. These changes include extreme increases in cell heights, complete loss of colloid and extreme hyperplasia, with the formation of new acini in the walls of preëxisting acini and large increases in the weights of the thyroid glands. These changes are proportional to the daily amounts of promizole administered.

2. Slight, but real, increases of the weights of the pituitary glands were usually observed. These increases, however, were not correlated with increases in thyroid gland weights and the conclusion that these increases were due to any hyperplasia of the basophilic cells in the anterior lobe or to increases in the thyrotropic hormone content was not demonstrated.

3. A decrease of the basal metabolic rates occurs in most animals made goitrous by promizole and the extent of depression of these rates was usually related to the degree of hyperplasia and to the loss of colloid from the thyroid acini.

4. Withdrawing promizole from the animals resulted in a recovery of the normal thyroid patterns and an elevation of the metabolic rates. Recovery, however, was not as rapid as that from effects of certain other goitrogens, for even 4 weeks after removal of the drug, normal cell colloid patterns were not restored.

5. These changes induced by promizole may be inhibited by giving thyroxin or desiccated thyroid but they are not inhibited by the administration of iodine. The conclusion seems indicated that promizole may interfere with the utilization of iodine by the thyroid and thus prevent the synthesis of thyroxine.

6. Promizole exerts an untoward effect on the hemopoietic system. Anemia, with lowered numbers of erythrocytes and concentrations of hemoglobin, was induced in young rats by amounts of the drug as low as 10 mg. Such changes were not observed to occur in adult rats that received 25 mg. daily.

7. Leukopenia and granulocytopenia were not induced in our animals by the amounts of the drug administered.

8. The drug induced considerable alopecia in growing animals fed purified diets, which did not occur in adult animals. Alopecia can be largely prevented by a dietary factor.

#### REFERENCES

1. ASTWOOD, E. B.: *J. Pharmacol. and Exp. Ther.*, **78**, 79, 1943.
2. ASTWOOD, E. B., and BISSELL, A.: *Endocrinology*, **34**, 282, 1944.
3. ASTWOOD, E. B., SULLIVAN, J., BISSELL, A., and TYSLOWITZ, R.: *Endocrinology*, **32**, 210, 1943.
4. BRATTON, A. C., and MARSHALL, E. K., JR.: *J. Biol. Chem.*, **128**, 537, 1939.
5. CHAPMAN, A., BALDES, E. J., and HIGGINS, G. M.: *Science*, **99**, 329, 1944.
6. FELDMAN, W. H., HINSHAW, H. C., and MANN, F. C.: *Proc. Staff Meet., Mayo Clin.*, **19**, 25, 1944.
7. FRANKLIN, A. L., LERNER, S. R., and CHAIKOFF, I. L.: *Endocrinology*, **34**, 265, 1944.
8. GORDON, A. S., GOLDSMITH, E. D., and CHARIPPER, H. A.: *Endocrinology*, **36**, 53, 1945.
9. GRIESBACH, W. E.: *Brit. J. Exp. Path.*, **22**, 245, 1941.
10. GRIESBACH, W. E., and PURVES, H. D.: *Brit. J. Exp. Path.*, **24**, 174, 1943.
11. HIGGINS, G. M.: *Proc. Staff Meet. Mayo Clin.*, **19**, 137, 1944.
12. HIGGINS, G. M., and INGLE, D.: Unpublished data.
13. KENNEDY, T. H., and PURVES, H. D.: *Brit. J. Exp. Path.*, **22**, 241, 1941.
14. LEE, M. O.: *Am. J. Physiol.*, **89**, 24, 1929.
15. MACKENZIE, C. G., and MACKENZIE, J. B.: *Endocrinology*, **32**, 185, 1943.
16. MACKENZIE, J. B., and MACKENZIE, C. G.: *Bull. Johns Hopkins Hosp.*, **74**, 85, 1944.
17. MARINE, D., BAUMANN, E. J., and CIPRA, A.: *Proc. Soc. Exp. Biol. and Med.*, **26**, 822, 1929.



18. MARINE, D., BAUMANN, E. J., WEBSTER, B., and CIPRA, A.: *Proc. Soc. Exp. Biol. and Med.*, 27, 1025, 1930.
19. MIXNER, J. P., REINEKE, E. P., and TURNER, C. W.: *Endocrinology*, 34, 168, 1944.
20. PURVES, H. D.: *Brit. J. Exp. Path.*, 24, 171, 1943.
21. RAWSON, R. W., HERTZ, S., and MEANS, J. H.: *Ann. Int. Med.*, 19, 829, 1943.
22. RAWSON, R. W., TANNHEIMER, J. F., and PEACOCK, W.: *Endocrinology*, 34, 245, 1944.
23. RICHTER, C. P., and CLISBY, K. H.: *Arch. Path.*, 33, 46, 1942.
24. SHARPLESS, G. R., PEARSONS, J., and PRATO, G. S.: *J. Nutr.*, 17, 545, 1939.
25. WEBSTER, B. and CHESNEY, A. M.: *Am. J. Path.*, 6, 275, 1930.
26. WEBSTER, B., CLAWSON, T. A., and CHESNEY, A. M.: *Bull. Johns Hopkins Hosp.*, 43, 278, 1928.
27. WHITEHEAD, V. I. E.: *Brit. J. Exp. Path.*, 24, 192, 1943.
28. WILLIAMS, R. H., WEINGLASS, A. R., BISSELL, G. W., and PETERS, J. B.: *Endocrinology*, 34, 317, 1944.

## INTERFERENCE BETWEEN INACTIVE AND ACTIVE VIRUSES OF INFLUENZA\*

### III. CROSS-INTERFERENCE BETWEEN VARIOUS RELATED AND UNRELATED VIRUSES

BY WERNER HENLE, M.D.

AND

GERTRUDE HENLE, M.D.

PHILADELPHIA, PA.

(From the Department of Pediatrics, School of Medicine, University of Pennsylvania,  
and the Children's Hospital of Philadelphia)

IN preceding papers it was shown that inactive influenza virus may interfere with the propagation of the homologous active agent in the allantoic cavity of the chick embryo.<sup>6,7,8</sup> When dialyzed allantoic fluids containing high titers of influenza virus were inactivated by ultraviolet irradiation for short periods of time and then injected either simultaneously with or at varying times prior to the administration of the active agent, no multiplication of virus took place during an incubationary period extending over 2 to 4 days. The allantoic fluids harvested from such eggs failed to agglutinate chicken red blood cells and were infective for the chick embryo only in low dilution. This low virus concentration in many cases constituted simply residual surviving virus from the second, *i. e.*, test virus injection. Marked reduction in the propagation of virus was noted when the inactivated agent was given as late as 3 hours following the active virus while a 24 hour delay of the injection of interfering fluid no longer affected the multiplication of the virus. Similar observations were reported subsequently by Ziegler, Lavin and Horsfall.<sup>14</sup>

These data suggested that interference takes place very rapidly, and further experiments demonstrated this point more clearly. Intra-allantoic injection of irradiated influenza virus just prior to or during flushing of the allantoic cavity with saline solution at a rate of 10 ml.

\* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Children's Hospital of Philadelphia.

per minute for 10 to 20 minutes produced marked interference with subsequently injected active virus.<sup>8</sup> This experiment showed also that the mere presence of the inactivated virus in the allantoic cavity was not responsible for the phenomenon since all excess of it was removed by the flushing procedure, but rather that some change must have occurred in the host by an interaction between the susceptible cells and the inactivated agent.

In addition to the speed of the reaction another property of the interference phenomenon in influenza appears of interest, *i. e.*, its relative non-specificity. Andrewes<sup>1</sup> observed interference between a neurotropic and non-neurotropic strain of influenza A virus. As pointed out in our preliminary note,<sup>6</sup> and in subsequent publications by others,<sup>13,14</sup> cross-interference was noted between influenza A and B virus and to some extent between these agents and swine influenza virus.

In the present paper data are summarized which were obtained in studies on cross-interference between inactivated and active human influenza viruses of Types A and B and porcine virus. In addition, evidence is presented to show that inactive influenza virus may interfere with the propagation of 2 biologically unrelated agents in the chick embryo.

**Methods and Materials.** All methods have been described in the previous papers of this series.<sup>7,8</sup> A few improvements of the techniques for the experiments with the viruses of equine encephalomyelitis and epidemic kerato-conjunctivitis are recorded in the text.

The viruses used were the PR-8, WS, F-12 and F-99 strains of influenza A, the Lee strain of influenza B and the S-15 strain of swine influenza virus. The PR-8 and Lee strains were obtained several years ago from Dr. Thomas Francis, Jr.; the WS strain from Dr. C. H. Andrewes; the S-15 strain, originally isolated by Dr. R. E. Shope, from Dr. W. M. Stanley; the F-12 and F-99 strains were isolated in this laboratory from fatal cases of influenza. The B-11 strain of Western equine encephalomyelitis, originally isolated by the Bureau of Animal Industry, was obtained from Dr. B. Hampil. A strain of epidemic kerato-conjunctivitis virus, originally isolated by Dr. Sanders,<sup>12</sup> was received from Dr. H. E. Calkins who had adapted the strain to the allantoic passage.<sup>3</sup> All viruses used have been passed by the allantoic route for at least 12 passages but not for more than 46 transfers.

**Experimental.** *Interference Between Various Influenza Viruses.* It has been found that influenza virus preparations inactivated by ultra-violet irradiation could be diluted usually 50- to 100-fold and still prevent the propagation of the homologous active agent in the allantoic cavity of the chick embryo to the extent that no measurable concentrations of hemagglutinin appeared in the allantoic fluid.<sup>8</sup> In the experiment summarized in Table 1 it is shown that the degree of interference is approximately the same regardless of whether the same or a different strain of the homologous type or a heterologous type of influenza virus was used as infecting agent. Groups of 40 10 day old chick embryos were injected with 1 ml. of dialyzed and irradiated PR-8 allantoic fluid in dilutions ranging from 1:9 to 1:243, using 3-fold steps, or with irradiated normal allantoic fluid in dilution 1:9 in saline solution. After 18 hours of further incubation at 36° to

37° C. 10 embryos of each group were infected with active PR-8 or WS virus of influenza A, or the Lee strain of influenza B, while a fourth group which did not receive any active virus served as control for the inactivated agent. The allantoic fluids were harvested 48 hours later and pooled according to the groups. No measurable hemagglutinin titers were found in any of the pools from the experimental groups injected with irradiated virus in dilutions up to 1:81 prior to the active agents. A dilution of 1:243 of the interfering fluid did not interfere to that extent with the production of hemagglutinin by these 3 virus strains, but all 3 groups showed a marked reduction in the hemagglutinin titer when compared with the results in control eggs, which had been injected with irradiated normal allantoic fluid instead of the irradiated virus preparation. Similar results were obtained when irradiated influenza B virus was injected prior to the 3 active agents.

TABLE 1.—QUANTITATIVE COMPARISON BETWEEN HOMOLOGOUS AND HETEROLOGOUS INTERFERENCE

First injection irradiated virus		Second injection active virus		Hemagglutinin titer 48 hours after second injection following injection of:				
				Irradiated virus in dilution				Normal allantoic fluid 1:9
Strain	Type	Strain	Type	1:9	1:27	1:81	1:243	
PR-8	A	PR-8	A	2	<2	<2	8	768
		WS	A	2	<2	<2	96	640
		Lee	B	<2	<2	<2	24	768
				<2	<2	<2	<2	
Lee	B	PR-8	A	<2	<2	32	256	768
		WS	A	2	<2	96	256	640
		Lee	B	<2	<2	4	192	768
				<2	<2	<2	<2	

TABLE 2.—CROSS-INTERFERENCE BETWEEN VARIOUS STRAINS OF INFLUENZA VIRUS TYPE A AND BETWEEN VARIOUS TYPES OF INFLUENZA VIRUS

First injection irradiated virus		Hemagglutinin titer 48 hours after second injection of active influenza virus					
		PR-8	WS	F-99	Lee	S-15	Saline
PR-8	A	<2	<2	<2	<2	<2	<2
WS	A	<2	<2	<2	<2	<2	<2
F-99	A	<2	<2	<2	<2	<2	<2
F-12	A	<2	<2	<2	<2	<2	<2
Lee	B	<2	<2	<2	<2	<2	<2
S-15	Swine	<2	<2	<2	<2	<2	<2
Normal allantoic fluid		512	768	192	384	128	

In the experiments cited in Table 1 the homologous interference reaction appeared slightly more pronounced than the cross-interference, since the hemagglutinin titers in the first positive series were lower than in the cases where the heterologous agents were used as test virus. However, other similar tests have not shown any degree of specificity and indeed the differences in the experiments cited fall well within the range of variation encountered in these experiments, when the titers of individual allantoic fluids are determined.

From the experiments recorded it appears that there are no marked

qualitative or quantitative differences between the interfering capacity toward homologous and heterologous active virus preparations. An extension of this finding is shown in Table 2 which summarizes an experiment employing 6 different irradiated virus strains which were tested each for their ability to interfere with 5 different active influenza virus strains. The interfering fluids were injected in sufficient dilution so as to prevent complications in the interpretation of the results by the presence in the allantoic fluids of measurable quantities of hemagglutinin administered with the primary injection of irradiated virus. A dilution of 1:3 to 1:9 sufficed in all cases to prevent agglutination of chick erythrocytes by the allantoic fluids harvested from the control eggs inoculated with the irradiated material only. Secondary injection of the various active virus preparations did not result in the production of hemagglutinin, *i. e.*, interference was marked in each instance. On the other hand, eggs previously treated with normal allantoic fluid developed the usual high titers of hemagglutinin following the injection of the active viruses. It should be pointed out that the PR-8 virus interfered with the strain of swine influenza virus used in the present experiment, in contrast to the experience reported by Ziegler *et al.*<sup>14</sup>

*Interference With Biologically Non-related Viruses.* Experiments on cross-interference between irradiated influenza viruses and other non-related agents were handicapped by the fact that the number of agents which have been adapted to passage by the allantoic route is limited. Two of these, the viruses of Western equine encephalomyelitis (WEE) and of epidemic kerato-conjunctivitis (EKC) were employed in a series of experiments. Preliminary tests with the WEE virus were found to yield quite irregular results until the technique of inoculation was changed so as to prevent infection of the tissues of the allantoic sac by the contaminated needle. The technique adopted was as follows: A small hole was drilled through the shell at the side of the egg over an area of the allantoic sac of 10 day old embryos free of larger blood-vessels. Another hole was made over the air sac. Undiluted irradiated influenza virus fluid was then injected in 0.1 ml. amounts through the side hole at a slow rate to prevent back-flow of the inoculum. The side hole was closed temporarily with Scotch tape and the eggs were returned to the incubator for 2 to 24 hours. After the side hole had been reopened, suction was applied to the hole over the air sac to permit air to enter into the allantoic cavity *via* the side hole. Thus a false air sac was created within the allantoic sac with the chorio-allantoic membrane still adhering to the shell membrane, in contrast to the usual false air sac method of Burnet<sup>2</sup> in which the false air sac is created over the intact, dropped membrane. The side hole was then enlarged to a diameter of about 3 mm. by means of a red hot iron rod. The heat coagulated the tissues surrounding the hole and rendered it presumably unsuitable for virus propagation. The WEE virus was then dropped into the allantoic cavity through the enlarged hole and the opening was sealed. The eggs were further incubated and candled at daily intervals until conclusion of the experiment, after

7 to 9 days. Control eggs were prepared in a similar manner except for the fact that irradiated normal allantoic fluid was injected instead of the inactivated virus.

Using this technique interference with the WEE virus gave more uniform results, showing in some instances 100% survival of the embryos for 9 days following injection of the agent. In other tests some embryos died, but usually much later than the corresponding controls. Experiments to illustrate these points are shown in Table 3. Attempts to demonstrate WEE virus in the allantoic fluids of some of the test embryos after 7 days of incubation failed. No tests at an earlier stage have been conducted.

TABLE 3.—INTERFERENCE BETWEEN IRRADIATED PR-8 VIRUS AND ACTIVE WESTERN EQUINE ENCEPHALOMYELITIS VIRUS

Exper. No.	First injection	Second injection active WEE virus LD <sub>50</sub>	Survival of chick embryos															
1	Irradiated PR-8 virus	100	D <sub>6</sub>	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
		10	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
	Irradiated normal allantoic fluid	100	D <sub>1</sub>	D <sub>1</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>
		10	D <sub>1</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>
	Irradiated PR-8	100	D <sub>6</sub>	D <sub>6</sub>	D <sub>6</sub>	D <sub>7</sub>	S	S	S	S	S	S	S	S	S	S	S	S
		10	D <sub>1</sub>	D <sub>6</sub>	D <sub>6</sub>	D <sub>7</sub>	D <sub>9</sub>	S	S	S	S	S	S	S	S	S	S	S
	Irradiated normal allantoic fluid	100	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>
		10	D <sub>1</sub>	D <sub>1</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>	D <sub>2</sub>

S = Embryo survived until experiment was discontinued (7 days in Experiment 1; 9 days in Experiment 2).

D<sub>1</sub> = Embryo died within 24 hours; D<sub>2</sub> = died between 24 and 48 hours; etc.

TABLE 4.—INTERFERENCE BETWEEN IRRADIATED PR-8 VIRUS AND ACTIVE VIRUS OF EPIDEMIC KERATO-CONJUNCTIVITIS

Exper. No.	First injection	Second injection active EKC virus in dilution	Survival of chick embryos															
1	Irradiated PR-8 virus	10 <sup>-1</sup>	D <sub>9</sub>	D <sub>9</sub>	S	S	S	S	S	S	S	S	S	S	S	S	S	S
		10 <sup>-2</sup>	D <sub>9</sub>	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
		10 <sup>-3</sup>	D <sub>1</sub>	D <sub>6</sub>	S	S	S	S	S	S	S	S	S	S	S	S	S	S
	Irradiated normal allantoic fluid	10 <sup>-1</sup>	D <sub>1</sub>	D <sub>1</sub>	D <sub>6</sub>	D <sub>6</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>
		10 <sup>-2</sup>	D <sub>1</sub>	D <sub>1</sub>	D <sub>6</sub>	D <sub>7</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>	D <sub>9</sub>
		10 <sup>-3</sup>	D <sub>1</sub>	D <sub>2</sub>	D <sub>6</sub>	D <sub>9</sub>	S	S	S	S	S	S	S	S	S	S	S	S
2	Irradiated PR-8 virus	10 <sup>-1</sup>	D <sub>1</sub>	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
		10 <sup>-2</sup>	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
	Irradiated normal allantoic fluid	10 <sup>-1</sup>	D <sub>1</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>
		10 <sup>-2</sup>	D <sub>2</sub>	D <sub>3</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>	D <sub>7</sub>

The same technique was employed for the study of interference between inactivated influenza virus and active EKC virus. As shown in Table 4 nearly all embryos inoculated with the EKC virus following normal allantoic fluid died or were found dead on opening of the eggs on the 7th or 9th day after the test injection. On the other hand, only very few of the embryos previously inoculated with interfering fluid failed to survive the injection of the EKC virus.

Other viruses have not been used as yet in interference experiments in the allantoic cavity. A few preliminary attempts were made, how-

ever, to study interference between irradiated influenza virus and vaccinia virus on the chorio-allantoic membrane. Although these tests seemed to indicate on occasion a slight reduction in pock counts, the tests on the whole were unsatisfactory, since the embryos frequently died when larger volumes of interfering fluid were used in order to flood the membrane, whereas smaller volumes were apparently insufficient to guarantee uniform spread of the interfering agent over the area of exposed membrane.

**Discussion.** The interference phenomenon between inactivated and active influenza viruses as described in this and previous papers,<sup>6,7,8</sup> reveals 2 properties which are noteworthy: (1) the reaction takes place very rapidly; and (2) it is relatively non-specific, *i. e.*, cross-interference occurs among all the influenza viruses tested regardless of the type. This is in contrast to the specificity of the immune response, where vaccination against one type protects only against infection with the type and not with the others. In addition, 2 other agents, the viruses of Western equine encephalomyelitis and of epidemic kerato-conjunctivitis, which are apparently biologically unrelated to the influenza agents, were prevented from exerting their fatal effect on the chick embryo by the previously injected irradiated influenza virus. Our findings with the WEE virus extend the observation by Duffy<sup>5</sup> who noted interference between active PR-8 virus and this agent provided enough head start was allowed for the spread of the influenzal infection.

These 2 properties of interference, the speed of the reaction and its non-specificity, should be of value in prophylaxis against influenza if the phenomenon could be made to serve this purpose, since no satisfactory method has been developed for the immediate protection of groups exposed to the disease. Whether or not the interference phenomenon may accomplish this aim remains to be seen. It is obvious that the experiments conducted in the allantoic cavity of the chick embryo are performed under particularly favorable conditions. The total surface of susceptible cells is comparatively small, the amount of interfering virus per unit surface is relatively large and the fluid content of the allantoic sac serves to spread the interfering agent uniformly to all susceptible cells. If one considers, on the other hand, the complicated structure of the mammalian respiratory tract the difficulties of reaching all susceptible cells become immediately apparent. The total surface is much larger and the volume of interfering fluid which can be safely administered, is relatively small. Correspondingly, interference experiments in mice did not yield as clear-cut results as those conducted in eggs although some evidence of the occurrence of the interference phenomenon in this species has been obtained. Obviously this problem requires further investigation.

Besides these practical considerations, some theoretical points may be discussed. Interference between various active related or unrelated viruses has been observed repeatedly.<sup>9,7</sup> In these instances frequently the view has been expressed that one virus may use up all essential metabolites required for the propagation of the other. Some

authors believe that pathologic changes in the host caused by one virus may prevent the spread of the other agent. Such explanations seem to be invalidated, however, by experiments in which inactivated virus was employed successfully as the interfering agent. Delbrück and Luria<sup>4,11</sup> concluded from studies on interference between 2 strains of bacteriophage that the agents compete for some substance within the cell, possibly a "key enzyme." Blocking of this enzyme by inactivated phage particles not only prevents the active agents from multiplying within the host but the host cell itself is markedly disturbed as seen by the fact that bacterial multiplication ceases.

Whether or not such marked changes occur in the tissues of the allantoic sac of the chick embryo following the injection of irradiated influenza virus is not yet known. As far as other cells are concerned, Hirst<sup>9</sup> has shown that chick erythrocytes are altered by contact with the influenza virus. After adsorption of the agent onto a hypothetical receptor on the surface of the cells, the virus is gradually released again into the surrounding medium. The red blood corpuscles are unable thereafter to adsorb new virus particles, supposedly because the receptor is destroyed in the reaction. It is worth noting, on the other hand, that virus preparations which have been irradiated for extended periods of time until the interfering capacity is lost, still may become attached to the red cells causing their agglutination.<sup>7,14</sup> Adsorption of virus onto the cells of the respiratory tract of the ferret occurs apparently in similar manner as in the case of red cells but elution has been noted only in the perfused excised lung, not in the respiratory tract of the living animal.<sup>10</sup> In the latter instance the reaction goes farther and the virus enters the cell with resulting multiplication of the agent. No information is available as to possible functional changes in these cells.

It is not possible, therefore, to state at present whether interference by the influenza viruses may be caused simply by blocking of some receptor spot on the surface of the susceptible cells, or whether the reaction occurs within the cells by interaction with some enzyme system. Whatever the mechanism may be, it is apparent from the results of the interference tests that the mode of infection by the human and porcine strains of influenza virus in the chick embryo is closely similar. This is not surprising since no marked differences in these agents have been noted in their biologic and physical behavior with the exception of their serologic specificity. No such close relationship can be claimed, however, between the influenza viruses and the agents of Western equine encephalomyelitis and of epidemic keratoconjunctivitis. Nevertheless, the results of the interference tests imply that these agents follow similar routes in the invasion of the chick embryo from the allantoic sac by occupying either the same receptor spots or by requiring in part the same enzyme systems for their propagation. It is conceivable that these results of cross-interference with unrelated agents may be obtained only in embryonic, *i. e.*, less differentiated cells and not in the tissues of the mature host. This question remains to be investigated.

**Summary.** Cross-interference in the allantoic cavity of the chick embryo between various strains of influenza A and one strain each of influenza B and swine influenza virus was studied. Virus preparations of one strain inactivated by ultraviolet irradiation interfered equally well with the propagation of the homologous and the heterologous active agents. In addition, irradiated influenza virus prevented death of the chick embryos from subsequent inoculation of the viruses of Western equine encephalomyelitis and of epidemic kerato-conjunctivitis.

#### REFERENCES

1. ANDREWES, C. H.: *Brit. J. Exp. Path.*, **23**, 214, 1942.
2. BURNET, F. M., and FARRIS, D. D.: *J. Bact.*, **44**, 241, 1942.
3. CALKINS, H. E.: *Proc. Soc. Exp. Biol. and Med.*, **56**, 46, 1944.
4. DELBRÜCK, M., and LURIA, S. E.: *Arch. Biochem.*, **1**, 111, 1942.
5. DUFFY, C.: *Science*, **99**, 517, 1944.
6. HENLE, W., and HENLE, G.: *Science*, **98**, 87, 1943.
7. HENLE, W., and HENLE, G.: *Am. J. Med. Sci.*, **207**, 705, 1944.
8. HENLE, W., and HENLE, G.: *Am. J. Med. Sci.*, **207**, 717, 1944.
9. HIRST, G. K.: *J. Exp. Med.*, **76**, 195, 1942.
10. HIRST, G. K.: *J. Exp. Med.*, **78**, 99, 1943.
11. LURIA, S. E., and DELBRÜCK, M.: *Arch. Biochem.*, **1**, 207, 1942.
12. SANDERS, M., and ALEXANDER, R. C.: *J. Exp. Med.*, **77**, 71, 1943.
13. ZIEGLER, J. E., JR., and HORSFALL, F. L., JR.: *J. Exp. Med.*, **79**, 361, 1944.
14. ZIEGLER, J. E., JR., LAVIN, G. I., and HORSFALL, F. L., JR.: *J. Exp. Med.*, **79**, 379, 1944.

## INTERFERENCE BETWEEN INACTIVE AND ACTIVE VIRUSES OF INFLUENZA\*

### IV. THE NATURE OF THE INTERFERING AGENT

BY GERTRUDE HENLE, M.D.

AND

WERNER HENLE, M.D.

PHILADELPHIA, PA.

(From the Department of Pediatrics, School of Medicine, University of Pennsylvania, and the Children's Hospital of Philadelphia)

It has been shown in previous publications of this series, and elsewhere, that intra-allantoic injection of influenza virus preparations inactivated by ultraviolet irradiation renders the tissues of the allantoic sac insusceptible to infection by the same route with homologous and heterologous strains of active influenza virus.<sup>6-9,20</sup> Allantoic fluids derived from normal chick embryos, or particulate components isolated from normal chorio-allantoic membranes, do not interfere with the propagation of the active agents.<sup>6,7</sup> The interfering agent is not dialyzable through cellophane and its concentration corresponds roughly to the quantity of virus present in the allantoic fluid.<sup>8</sup> However, various observations indicate that it is difficult to study quantitatively the relation between virus concentration and interfering capacity, since ultraviolet irradiation causes progressive changes in the virus

\* The work described in this paper was done under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Children's Hospital of Philadelphia.



preparations.<sup>7,20</sup> First, the infectivity decreases rapidly and the fluid finally becomes non-infective while the interfering capacity is reaching its peak. On further irradiation the property of interference diminishes and disappears completely while the hemagglutinating activity of the virus is still intact. The latter property is lost only on prolonged treatment with ultraviolet light. These various stages in the process of inactivation may overlap to a certain extent. Furthermore, the effectiveness of irradiation is dependent to some degree on the composition of the allantoic fluids. The presence of certain low molecular weight substances removable by dialysis as well as the age of the embryo from which the fluids are obtained influence the conditions for inactivation markedly.<sup>7</sup> Finally, inactive virus has been found to accumulate spontaneously in the allantoic fluids with increasing time of incubation of the egg cultures, and this cannot readily be assayed.<sup>7</sup> Therefore, in order to study the nature of the interfering agent more extensively and to prove its identity with the inactivated virus it was necessary to resort to other means. Experiments employing physical and immunologic techniques, which had been mentioned briefly in a previous publication of this series<sup>8</sup> are summarized in the present paper.

**Materials and Methods.** All techniques for the preparation and assay of virus and the methods used in the interference test in chick embryos have been described previously.<sup>7,8</sup> They will be extended when required in the text.

**Centrifugation.** A mechanically driven high speed centrifuge developed by Rawson, Scherp and Lindquist<sup>15</sup> was used in these experiments.

**Immune Sera.** Human hyperimmune serum against influenza A virus (PR-8) and experimental human convalescent serum to influenza B (Lee) were used for the neutralization of interference. Sera taken before vaccination or infection served as controls. The sera were tested for potency by the inhibition of red cell agglutination according to the method of Hirst.<sup>11</sup>

**Experimental.** 1. *Sedimentation by High Speed Centrifugation.* It has been shown by several authors that influenza viruses may be sedimented in the high speed centrifuge at relatively low speeds<sup>2,13</sup> since they possess sedimentation constants of about 600 S.<sup>5,16,17,18</sup> In addition, a smaller component with a sedimentation constant of about 30 S has been found<sup>1,17</sup> which shows antigenic activity in the complement fixation test.<sup>10</sup> A study of the interfering property of the various fractions obtained by the centrifugation method was undertaken and the following protocol serves as an example for these experiments.

Ten-day old chick embryos were inoculated with influenza B virus (Lee) and the allantoic fluids were harvested 72 hours after inoculation. After removal of the coarse particles in the angle centrifuge, a small sample of the preparation was retained while the remainder was centrifuged in the high speed centrifuge at 20,000 r.p.m. for 20 minutes. The sediment contained the bulk of the virus and was resuspended in normal allantoic fluid. This preparation will be referred to as 600 S component.<sup>5,16-18</sup> Part of the supernatant fluid of the 20,000 r.p.m. run was saved, while the remainder was subjected to high speed centrifugation at 30,000 r.p.m. for 60 minutes. The supernatant fluid was

saved and the sediment was resuspended in normal allantoic fluid and re-centrifuged at 20,000 r.p.m. for 20 minutes to remove additional 600 S material. This fraction was called 30 S component.<sup>1,10,17</sup> All 5 preparations, the original allantoic fluid, samples of the supernatant fluids from the centrifuge runs at 20,000 and 30,000 r.p.m., and the 600 S and 30 S materials suspended in normal allantoic fluid, were dialyzed in the same bath overnight against 20 volumes of M/100 phosphate buffered saline solution of pH 7.1. Before irradiation the materials were centrifuged at low speed to remove a few larger aggregates. The preparations were then irradiated by ultraviolet light for 3 minutes in a manner previously described,<sup>7</sup> and tested for their capacity to agglutinate chick red cells<sup>11</sup> and to interfere with the propagation of active Lee virus. For the latter test active homologous virus (or saline solution in controls) was injected 6 hours following the primary injection of the irradiated materials in varying dilutions. The results of these tests are summarized in Table 1.

TABLE 1.—SEDIMENTATION OF THE INTERFERING AGENT BY HIGH SPEED CENTRIFUGATION

First injection			Hemagglutinin titer 48 hours after 2nd inoculation following injection of irradiated materials in dilutions						
Irradiated material	Hemaggl. titer	Second injection	Undil.	1:3	1:9	1:27	1:81	1:243	1:729
Original allantoic fluid	448	Virus Saline	..	..	<2	<2	<2	14	112
			..	..	<2	<2	<2	<2	<2
Supernatant 20,000 r.p.m.	28	Virus Saline	..	<2	<2	28	112	.	.
			..	<2	<2	<2	<2		
Supernatant 30,000 r.p.m.	<2	Virus Saline	48	128					
			<2	<2					
600 S 2 times concentrated	768	Virus Saline	..	..	<2	<2	<2	28	32
			..	..	<2	<2	<2	<2	<2
30 S 5 times concentrated	8	Virus Saline	<2	64					
			<2	<2					
Normal allantoic fluid	<2	Virus	192						

As seen in the table, the results of interference corresponded to those of the hemagglutination test. Centrifugation at 20,000 r.p.m. removed more than 90% of the hemagglutinins and interference was decreased to about the same extent. On the other hand, the sediment resuspended to one-half of the original volume of allantoic fluid came up to the hemagglutinating titer and interfering capacity of the original allantoic fluid. Centrifugation at 30,000 r.p.m. removed the remaining hemagglutinins sufficiently to render the test negative and interference was practically absent. The 30 S material still contained a low titer of hemagglutinin due to residual 600 S material<sup>17</sup> and interference was correspondingly present but slight. The allantoic fluids from control eggs inoculated with the irradiated preparation in this and the following experiments prior to injection with saline solution, instead of active virus, revealed no measurable hemagglutinins, indicating that the irradiated preparations had lost their infectivity. This was substantiated in some of the experiments by passage of these fluids to new chick embryos.

From these data, it is apparent that the interfering capacity is

closely linked with the agglutinating property which in turn has been found to be inseparable from the virus particle.<sup>5,11,12,14,16-18</sup>

2. *Adsorption Onto and Elution From Chick Red Cells.* It had been noted by Hirst<sup>12</sup> that both active and inactive influenza virus is readily adsorbed onto chick red cells and eluted therefrom. This property has been utilized for the production of concentrated influenza vaccine.<sup>3</sup> The question arose whether the interfering property would be adsorbed and eluted in the same manner as the active or inactivated virus and the following protocol exemplifies such an experiment.

Allantoic fluids were harvested from chick embryos which had been infected 48 hours previously with the PR-8 virus of influenza A. After preliminary centrifugation to remove coarser particles from the fluid a small sample was saved while the remainder was cooled to 0° C. in an ice-water bath. Sterile washed chick erythrocytes were added to form a 5% suspension. After 30 minutes at 0° C., the mixture was centrifuged in chilled cups for 10 minutes at 2000 r.p.m. and the supernatant fluid removed. The sediment was resuspended in one-half the original volume of normal allantoic fluid and placed into a water bath at 37° C. for 2½ hours. The red cells were then sedimented by centrifugation and the supernatant fluid containing the eluted virus saved. The 3 preparations, the original allantoic fluid, the absorbed supernatant fluid and the eluate, were dialyzed and irradiated in a manner similar to that described in the centrifugation experiment. Hemagglutination and interference tests have yielded the results recorded in Table 2.

TABLE 2.—ADSORPTION OF THE INTERFERING AGENT ONTO AND ELUTION FROM CHICK RED BLOOD CELLS

First injection		Second injection	Hemagglutinin titer 48 hours after 2nd inoculation following injection of irradiated virus in dilution				
Irradiated material	Hemaggl. titer		1:3	1:9	1:27	1:81	1:243
Original allantoic fluid	512	Virus	..	<2	<2	<2	16
		Saline	..	<2	<2	<2	<2
Supernatant after adsorption	32	Virus	<2	2	64	384	
		Saline	<2	<2	<2	<2	
Eluate 2 times concentrated	512	Virus	..	<2	<2	<2	16
		Saline	..	<2	<2	<2	<2
Normal Allantoic fluid	<2	Virus	384				

As seen in the table more than 90% of the hemagglutinins were removed from the allantoic fluid by adsorption onto the red cells and the results of the interference test show a similar decrease in activity. On the other hand, the eluate contained most of the agglutinating property and the interference test was similar in strength to that obtained with the original allantoic fluid. This experiment shows then that the interfering property reacts similarly to the hemagglutinating agent of an influenza virus preparation in being adsorbed onto and eluted from chick red cells.

3. *Specific Neutralization of Interference by Immune Sera.* The fact that influenza virus Type A interferes equally well with Type B, and conversely,<sup>6,9,19,20</sup> permits the testing of the effect of specific immune

sera on the interfering capacity of an irradiated virus preparation. Antibodies to influenza virus react highly specifically and no cross-neutralization occurs between Type A and B viruses.<sup>4</sup> Consequently, tests on the neutralization of the interfering property by specific immune sera are not complicated by residual unattached antibodies injected together with the inactivated virus, as long as the heterologous active agent is used for the test of interference. Such an experiment is summarized in the following protocol.

Allantoic fluid infected with influenza A virus (PR-8) and inactivated by ultraviolet irradiation was mixed with either pooled human hyperimmune serum against influenza A virus in dilution 1:4 or with pooled serum taken from some of the individuals before immunization, equal volumes of allantoic fluid and diluted serum being used. Control preparations were made by adding normal allantoic fluid instead of the virus preparation to the sera. These 4 preparations were tested both for hemagglutination and interference. Influenza B virus (Lee) served as the test agent for the interfering capacity of the irradiated influenza A virus-serum mixtures, injected in varying dilutions. The results of these tests are shown in Table 3.

TABLE 3.—NEUTRALIZATION OF THE INTERFERING AGENT BY IMMUNE SERUM

First injection		Hemaggl. titer	Second injection	Hemagglutinins 48 hours after 2nd inoculation of active influenza B (Lee) virus following primary injection of the various mixtures in dilution (in terms of allantoic fluid)			
Virus	Serum			1:9	1:27	1:81	1:243
Influenza A (PR-8)	Anti-A	<2	Virus	12	128	512	768
			Saline	<2	<2	<2	<2
Influenza A	Normal	256	Virus	<2	<2	<2	12
			Saline	<2	<2	<2	<2
Normal allantoic fluid	Anti-A	<2	Virus	384	512	384	512
			Saline	<2	<2	<2	<2
Normal allantoic fluid	Normal	<2	Virus	384			

As can be seen in the table the addition of a high titered anti-influenza A serum to inactive influenza A virus preparations neutralized completely the hemagglutinins and its interfering capacity with active influenza B virus was reduced extensively as compared with the effect of pre-vaccination serum. Neither the hyperimmune nor control sera contained sufficient concentrations of anti-influenza B antibodies, in the dilutions used, to prevent the multiplication of this agent in the allantoic cavity, as measured by hemagglutinin titers.

Similar experiments with B convalescent serum and irradiated B virus have shown neutralization of the interfering property with the active influenza A virus. These data show clearly that the immune sera contained antibodies neutralizing the interfering property, presumably by preventing attachment of the irradiated virus to the susceptible host cell.

**Summary.** Although it was apparent that the interfering capacity of irradiated influenza virus preparations corresponds within certain limits to their content of virus, this observation would not exclude the possibility that the interfering substance might be a product of the

virus or the infected host cell and not the inactivated agent. However, the experiments related in this paper serve to identify the interfering agent with the inactive virus. The interfering substance behaves in every respect tested like the influenza virus. It is sedimented in the high speed centrifuge under conditions which will sediment the active virus. It is adsorbed onto and eluted from chicken red cells in amounts comparable to the virus and, finally, it is specifically neutralized by immune sera, *i. e.*, the interfering agent of influenza A preparations by anti-influenza A serum only and not by anti-B serum, and the B preparations by anti-influenza B serum and not by anti-A serum.

## REFERENCES

1. CHAMBERS, L. A., HENLE, W., LAUFFER, M. A., and ANDERSON, T. F.: *J. Exp. Med.*, **77**, 265, 1943.
2. ELFord, W. J., and ANDREWES, C. H.: *Brit. J. Exp. Path.*, **17**, 422, 1936.
3. FRANCIS, T., JR., and SALK, J. E.: *Science*, **96**, 499, 1942.
4. FRANCIS, T., JR.: *Science*, **92**, 405, 1940.
5. FRIEDEWALD, W. F., and PICKELS, E. G.: *J. Exp. Med.*, **79**, 301, 1944.
6. HENLE, W., and HENLE, G.: *Science*, **98**, 87, 1943.
7. HENLE, W., and HENLE, G.: *Am. J. Med. Sci.*, **207**, 705, 1944.
8. HENLE, W., and HENLE, G.: *Am. J. Med. Sci.*, **207**, 717, 1944.
9. HENLE, W., and HENLE, G.: *Am. J. Med. Sci.*, **210**, 362, 1945.
10. HENLE, W., and WIENER, M.: *Proc. Soc. Exp. Biol. and Med.*, **57**, 176, 1944.
11. HIRST, G. K.: *J. Exp. Med.*, **75**, 49, 1942.
12. HIRST, G. K.: *J. Exp. Med.*, **76**, 195, 1942.
13. HOYLE, L., and FAIRBROTHER, R. W.: *J. Hyg., Cambridge, Eng.*, **37**, 512, 1937.
14. MCCLELLAND, L., and HARE, R.: *Canad. Publ. Health J.*, **32**, 530, 1941.
15. RAWSON, A. J., SCHERP, H. W., and LINDQUIST, F. E.: *J. Bact.*, **40**, 657, 1940.
16. SHARP, D. G., TAYLOR, A. R., McLEAN, I. W., JR., BEARD, D., BEARD, J. W., FELLER, A. E., and DINGLE, J. H.: *J. Immunol.*, **48**, 129, 1944.
17. STANLEY, W. M.: *J. Exp. Med.*, **79**, 267, 1944.
18. TAYLOR, A. R., SHARP, D. G., BEARD, D., BEARD, J. W., DINGLE, J. H., and FELLER, A. E.: *J. Immunol.*, **47**, 261, 1943.
19. ZIEGLER, J. E., and HORSFALL, F. L., JR.: *J. Exp. Med.*, **79**, 361, 1944.
20. ZIEGLER, J. E., LAVIN, G. I., and HORSFALL, F. L., JR.: *J. Exp. Med.*, **79**, 379, 1944.

## METHIONINE IN THE TREATMENT OF TOXIC HEPATITIS

By JAMES H. EDDY, JR., M.D.\*

SHREVEPORT, LA.

(From the Medical Department of The Louisiana Ordnance Plant)

THE increased sensitivity of the liver to toxins, following depletion of the protein stores, has been well demonstrated by Miller and Whipple<sup>8</sup> in their experiments on dogs exposed to chloroform. They found that normal dogs that are well fed will tolerate 1 hour of surgical chloroform anesthesia, but when the dogs are fasted for 3 days preceding the anesthesia, there will always be marked hyaline central necrosis of the liver. In these cases the central necrosis usually involved 50 to 70% of the cells in each lobule and occasionally the exposure caused death in from 2 to 4 days. The protective action of protein diets had previously been pointed out by Goldschmidt, Vars and Ravdin<sup>9</sup> in their work with mice.

\* We are indebted to Wyeth Incorporated for a supply of Methionine used in some of these cases.

The value of carbohydrate in protecting the liver has widespread acceptance. In view of recent studies on protein factors in liver protection it is likely, as pointed out by Miller and Whipple,<sup>9</sup> that its efficiency is due primarily to sparing protein stores.

The interest in dietary factors in protection against liver injury received more attention following the reports of several groups concerned with the identification of the specific protein factor responsible for liver protection. Miller, Ross and Whipple<sup>7</sup> demonstrated in 1940 that the amino acid, methionine, and to a less extent cystine, gave protection against liver injury if given before chloroform anesthesia. These materials were shown to be as effective as the feeding of a large protein meal. In the same study it was shown that a number of non-sulfur containing amino acids lacked this protective quality. Later, in 1942, Miller and Whipple<sup>9</sup> showed that protein depleted animals could be protected against chloroform anesthesia even when methionine was given 3 to 4 hours after exposure to chloroform. If, on the other hand, the methionine was given as late as 6 hours after anesthesia, all of the animals died. Apparently by that time all of the cells were fatally damaged. In other words, it is necessary that some viable liver tissue be present if methionine is to be of value in protecting the liver. This points to the clinical value of early treatment if methionine is to have maximum efficiency. The uselessness of choline alone in attempts to protect the liver has been pointed out by several investigators. When the choline was given with cystine there appeared to be equally as much benefit as when methionine was given.

In 1944 Goodell, Hanson and Hawkins<sup>4</sup> demonstrated again the increased susceptibility of protein depleted dogs to hepatotoxins. They used mapharsen in large doses as the toxic agent. This group also demonstrated the effectiveness of methionine in protecting these animals against the poison. In this report it was noted that oral administration of 2 to 4 gm. of methionine 20 to 40 hours prior to giving the arsenical was more effective in protecting the liver than was the intravenous administration of 1 gm. of amino acid just prior to giving mapharsen. Unfortunately it is difficult to tell whether the time element, the increase in dosage or the route of administration is the most important factor.

The manner in which methionine protects the animal against liver damage is not clear but there is evidence to support the belief that its value depends primarily on the sulfur content of the amino acids. Weight is given to this concept by the work of Miller and Whipple<sup>9</sup> in which they demonstrated that the animal that has been depleted of protein has been more completely depleted of sulfur. They believed that this indicated a "definite loss by the protein depleted liver of some relatively sulfur rich component, presumably protein in nature, the loss of which makes the liver more susceptible to a variety of injurious agents known and unknown."

Heppel *et al.*<sup>6</sup> in January of this year reported on the influence of dietary factors in the toxicity of dichloroethane. They pointed to the decreased resistance to the toxic action of dichloroethane among ani-

mals on a protein deficient diet but showed that these animals resisted the toxic action if they were supplied with methionine and choline. They did emphasize, however, that dichloroethane did not produce hepatic lesions such as those described following chloroform or carbon tetrachloride exposure. They remarked that, "The appearance of livers of rats dying after dichloroethane showed nothing to distinguish them from the livers of rats fed similar diets but not exposed." This is somewhat suggestive that the protective action of methionine may be dependent not alone on the liver. The appearance of adrenal changes in some of their experimental animals may be of some significance.

Much of the recent clinical interest in methionine followed the report of Gyorgy<sup>5</sup> in 1944. In that report Gyorgy reviewed the work leading up to the acceptance of methionine as the specific dietary factor in the prevention of liver damage. In discussing many of the so-called hepatotoxins the strong importance of dietary factors was brought out.

Gyorgy outlined the progression of changes in the liver of animals on a protein deficient diet from fatty infiltration through necrosis and to cirrhosis. He pointed out, too, the presence of the pigment "ceroid" in the cirrhotic liver that has been produced by purely dietary means, and remarked that "ceroid" has not been seen in other forms of cirrhosis in animals or man. The appearance of kidney lesions simultaneously with the liver damage on a purely dietary basis was compared with the so-called hepatorenal syndrome in man. In discussing the similar protection offered the liver by methionine and by choline plus cystine, Gyorgy suggested that choline and cystine are needed for the synthesis of another substance that may be methionine. Specific recommendations for the use of methionine or cystine plus choline in the prevention and treatment of hepatic injury due to purely toxic as well as dietary factors were made.

The dietary factor in connection with hepatotoxins has been pointed out recently in a paper from this department on the occurrence of carbon tetrachloride poisoning.<sup>2</sup> It was noted that all of the severe cases of poisoning appeared in Negro women who were known to exist on a high fat and protein deficient diet. Although many white employees worked at the same job and had mild toxic symptoms, not one of their group showed any serious damage.

The report by Beattie *et al.*<sup>1</sup> of 1 case of carbon tetrachloride hepatitis treated with methionine led to our investigation of the value of this material in the treatment of hepatitis due to trinitrotoluene. This work has led to study on its use in other types of hepatitis and in cirrhosis.

Our work began in July 1944 and since that time we have treated 30 cases of acute toxic hepatitis with methionine. Most of these cases have been caused by trinitrotoluene and at least 10 of them have been seriously ill. To this date there have been no fatalities. This is of interest in view of the published mortality in T.N.T. hepatitis of 30 to 35%. It is also noteworthy that of our 2 cases of T.N.T. hepat-

itis seen prior to using methionine 1 patient died and the second had a prolonged illness. Many of the patients since that time have appeared to be as severely poisoned as were the first cases on their admission.

Among our cases of toxic hepatitis treated with methionine, the length of hospitalization varied from 4 days to 7 weeks with an average of 13 days. The diagnosis was based on an analysis of the occupational exposure, physical examination, icterus index, Hanger Cephalin Flocculation test, and urinalysis for urobilinogen and bilirubin. These examinations almost always supported each other and they gave an excellent method of follow-up for the cases. We are particularly impressed by the value of a daily urinalysis for urobilinogen and bilirubin in that it has followed the patient's course much closer than other examinations and is so easily done. We have noted that the decrease in bile in the urine and increase in urobilinogen are followed closely by a decrease in the icterus index but that the decrease is rather slow below 20 units and often shows a value of 10 to 12 units for several months. The Hanger Cephalin Flocculation test has never given a false negative and false positives have been rare in our experience. We do not, however, consider a reading of + or ++ as of any significance. This test has been rather slow to return to normal but usually shows a quantitative change before the patient leaves the hospital and becomes negative after 1 or 2 months.

Almost all of these patients complained of dizziness, nausea, vomiting, weakness and upper right quadrant pain. The physical examination showed principally jaundice and an enlarged liver. The patients have been white and colored, and male and female with a preponderance of white males.

Treatment has consisted of bed rest, a diet rich in protein and carbohydrate and poor in fat, administration of multiple vitamin product plus added vitamin B complex and the oral administration of methionine in doses of from 3 to 8 gm. daily. The average dose was 3 to 4 gm. per day but in 2 of these cases the patients showed more jaundice and the dose was increased to 8 gm. daily and the patients fed by duodenal tube. In both of these cases improvement was marked after 48 hours.

Several of these T.N.T. cases are outlined as typical of the more severe type that we have seen here.

**Case Abstracts.** CASE 1. V. L., a white female, had been working in a thread cleaning operation with trinitrotoluene for 2 months when she began to complain of weakness, upper right quadrant pain, nausea and vomiting and after a few days noted a yellow color in her skin. She stayed home from work for a few days and went to her family physician who made a diagnosis of toxic hepatitis and referred her to this hospital. Examination on admission revealed a slender young woman who was deeply jaundiced. Vomiting was severe and the patient was nauseated almost constantly. The liver was enlarged to 4 cm. below the costal margin and was tender. There were no other physical findings of note.

The icterus index was 63.3 and the Hanger Cephalin Flocculation test was ++++ in 24 hours. The urine gave a ++ test for bile and the urobilinogen



was present in a dilution of 1 to 200. There were 3,790,000 red cells with 10.4 gm. of hemoglobin. The total white cell count was 3800 with 49 polymorphonuclears, 39 lymphocytes and 12 mononuclears. The platelet count was 225,000.

She was given a diet high in protein and carbohydrate and low in fat. This was supplemented with vitamins and 3 gm. of methionine daily.

Clinical improvement was rapid and the patient was able to leave the hospital after only 8 days. She returned for observation after 30 days at which time the laboratory reports showed an 8.4 icterus index and no bile in the urine. The urobilinogen was decreased in amount. The Hanger test was ++ at the end of 24 hours and +++ at 48 hours.

CASE 2. R. W., a colored male, 26 years of age, came to the hospital on Nov. 20, 1944, complaining of weakness, dizziness and jaundice. This man had been exposed to T.N.T. for 5 months. He was deeply jaundiced and appeared seriously ill. Examination showed an enlarged tender liver but no other masses or enlarged organs. There was no edema and no evidence of hemorrhage.

The icterus index was 56 on admission. There was ++++ bile in the urine and the urobilinogen was decreased in amount. The Hanger Cephalin Flocculation test was +++. The blood count was essentially normal.

Treatment was begun with methionine in doses of 1 gm. 3 times daily and he was also given methenamine, the vitamins and a diet rich in protein and carbohydrate and low in fat. The patient progressed very poorly and after 3 days he vomited frequently so that it was necessary to give his diet and medication by duodenal tube. He improved slightly for a short time but then appeared to be going down hill rapidly so that by Dec. 4, 1944, his icterus index was 112.4 and he was comatose. At this time the dose of methionine was increased to 2 gm. 4 times daily and feedings were given every hour. Improvement occurred shortly after this change and by Dec. 20 the icterus index was 52 and the dose of methionine was returned to the original amount. He was discharged as well on Jan. 9, 1945. At that time his fasting icterus was 17.8 and his Hanger test was +. About 1 month later his icterus index was 10. This has been one of our more seriously ill patients and one who I feel was helped considerably by methionine.

CASE 3. G. N., a 45 year old white male, who had been exposed to T.N.T. for 13 months came to the hospital in the middle of February complaining of generalized aching, sleeplessness and a feeling that his right hand was swollen. Examination of the urine at that time showed a normal amount of urobilinogen and no bile. He continued at his work and 3 days later he noted a diarrhea. On Feb. 23 he came in complaining of weakness, epigastric pain and said that he had passed numerous tarry stools. He had 2.5 million red cells and 9.2 gm. of hemoglobin. A diagnosis of bleeding duodenal ulcer was made and he was referred to a local sanatorium. He improved rapidly but on March 8, 1945, his physician noted some yellowish discoloration of the sclerae and referred him to us for laboratory study. At that time his icterus index was 20 and the Flocculation test was +++.

We were not able to get him back to the hospital until March 15, at which time he was hospitalized. The icterus index had reached 56 and the urine showed ++++ bile with a 1 to 40 dilution of urobilinogen. The Hanger test was +++. The treatment of this patient was started the same as the previous ones with the addition of ferrous sulfate for his anemia and tincture of belladonna and an alkali for his ulcer.

This patient got along rather poorly with his icterus index gradually increasing, the urine showing a great deal of bile and the urobilinogen decreasing until only a trace was found. The urobilinogen never entirely disappeared. Roentgen ray of the gall bladder region showed no opaque calculi. By March 24 the icterus index was 83.3 and the patient was given vitamin K by mouth. Because of the atypical history in this case a study of the gall bladder region following the oral administration of "Priodax" was attempted. No gall

bladder shadow was seen and the patient seemed worse after this study. He vomited frequently and was drowsy. Tube feeding was given until nausea subsided and then oral feeding was offered every 2 hours. The methionine was increased to 2 gm. 4 times daily. At this time the icterus index was 129 and the patient appeared to be losing ground rapidly. Following the changes in his medication he began to improve rapidly and after 7 days the icterus index was 51 and the patient was enjoying his food. Approximately 1 month after his jaundice was discovered his icterus index was 23.5, the urine was normal and the Hanger Flocculation test was still + + + +.

The remarkable improvement in 2 of these patients when the dose of methionine was increased has led us to believe that our usual dose of methionine may be inadequate and we should possibly consider that 6 to 8 gm. daily be given to all seriously sick patients. We have not hesitated to give 12 gm. daily to 1 patient who appeared to be in extremely poor condition. Our present routine is to start these patients on smaller doses and to increase the amount if clinical improvement is not easily apparent.

Two patients with epidemic hepatitis have been given methionine and improvement has been striking within 48 hours. In 1 of these patients the jaundice returned when treatment was stopped but responded quickly when methionine was given again.

Several cases of acute carbon tetrachloride hepatitis treated with methionine have been reported in an earlier paper. One of these cases came to the hospital in a coma. Her liver was enlarged to below the umbilicus, was soft and tender and her icterus index was 344. She was given 12 gm. of methionine daily and improved rapidly so that after 4 weeks the icterus index had returned to 15.

Treatment of a few patients with known cirrhosis of the liver has been started and several remarkable observations have been made in these cases. It is, however, too early and the number of cases under treatment has been too few to draw any conclusions from this work. It appears that methionine or choline plus cystine will be of value in early cirrhosis and in controlling the episodes of acute activity in older cases. It is apparent that little help can be given to the far advanced cases as by that time the functional unit has been irreparably embarrassed by the laying down of scar tissue.

**Summary and Conclusions.** The results of animal experiments indicate the value of methionine in protecting the liver from damage by certain hepatotoxic drugs.

Its effectiveness in treating toxic hepatitis is shown in a group having hepatitis due to trinitrotoluene. In these cases there have been no fatalities and the course of the illness is believed to have been shortened appreciably.

Several other cases of hepatitis due to carbon tetrachloride and 2 patients with epidemic hepatitis are thought to have been improved by methionine.

There has been no evidence of toxic reactions to methionine and further clinical trial is urged.

## REFERENCES

1. BEATTIE, J., HERBERT, P. H., WECHTEL, C., and STEELE, C. W.: Studies on Hepatic Dysfunction: Carbon Tetrachloride Poisoning Treated With Casein Digest and Methionine, *Brit. Med. J.*, 1, 209, 1944.
2. EDDY, J. H.: Carbon Tetrachloride Poisoning a Preliminary Report on the Value of Methionine in Hepatitis, *J. Am. Med. Assn.* (to be published).
3. GOLDSCHMIDT, S., VARS, H. M., and RAVDIN, I. S.: The Influence of Foodstuffs Upon the Susceptibility of the Liver to Injury by Chloroform, and the Probable Mechanism of Their Action, *J. Clin. Invest.*, 18, 277, 1939.
4. GOODELL, J. P. B., HANSON, P. C., and HAWKINS, W. B.: Methionine Protects Against Mapharsen Liver Injury in Protein-depleted Dogs, *J. Exp. Med.*, 79, 625, 1944.
5. GYORGY, P.: Experimental Hepatic Injury, *Am. J. Clin. Path.*, 14, 67, 1944.
6. HEPPEL, L. A., NEAL, P. A., DAFT, F. S., ENDICOTT, K. M., ORR, M. L., and PORTERFIELD, V. T.: Toxicology of 1,2-Dichloroethane (Ethylene Dichloride); II. Influence of Dietary Factors on the Toxicity of Dichloroethane, *J. Ind. Hyg. and Tox.*, 27, 15, 1945.
7. MILLER, L. L., ROSS, J. F., and WHIPPLE, G. H.: Methionine and Cystine, Specific Protein Factors Preventing Chloroform Liver Injury in Protein-depleted Dogs, *Am. J. Med. Sci.*, 200, 739, 1940.
8. MILLER, L. L., and WHIPPLE, G. H.: Chloroform Liver Injury Increases as Protein Stores Decrease: Studies in Nitrogen Metabolism in These Dogs, *Am. J. Med. Sci.*, 109, 204, 1940.
9. MILLER, L. L., and WHIPPLE, G. H.: Liver Injury, Liver Protection, and Sulfur Metabolism: Methionine Protects Against Chloroform Liver Injury Even When Given After Anesthesia, *J. Exp. Med.*, 76, 421, 1942.

# PROGRESS OF MEDICAL SCIENCE

## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

G. LYMAN DUFF, M.A., M.D., PH.D.

STRATHCONA PROFESSOR OF PATHOLOGY, MC GILL UNIVERSITY

AND

E. G. D. MURRAY, O.B.E., M.A., L.M.S.S.A., F.R.S.C.

PROFESSOR OF BACTERIOLOGY AND IMMUNITY, MC GILL UNIVERSITY  
MONTREAL, CANADA

---

### THE PATHOLOGY OF THE PANCREAS IN EXPERIMENTAL DIABETES MELLITUS

By G. LYMAN DUFF, M.A., M.D., PH.D.

(From the Department of Pathology, Pathological Institute, McGill University)

WITHIN recent years two new forms of experimental diabetes have been discovered, that produced by anterior pituitary extracts and that produced by alloxan. Both have been studied intensively from the physiologic and morphologic points of view and a considerable mass of experimental data has rapidly accumulated. It seems timely, therefore, to look back over the whole field of experimental diabetes, including that form of the experimental disease originally produced by complete or partial pancreatectomy, with a view to summarizing the essential observations. In this review an attempt is made to give such a retrospect of the morphologic aspects of this field with particular reference to changes in the islets of Langerhans of the pancreas. Physiologic observations have not been by any means excluded but, in the main, only those are cited that have a bearing on the pathogenesis of the lesions described or on the interpretation of their significance.

**Diabetes Produced by Partial Pancreatectomy.** Diabetes mellitus was first produced experimentally in dogs by von Mering and Minkowski<sup>60</sup> in 1889 by means of total extirpation of the pancreas. Minkowski<sup>61</sup> also found that no diabetes resulted if one-fourth to one-fifth of the pancreas were left in position. He and other investigators showed that when smaller parts of the pancreas were left, diabetes of varying grades of severity might develop, but if more than one-tenth of the gland were left in functional condition there was no certainty of diabetes developing. Sandmeyer,<sup>57</sup> however, was able to demonstrate that severe diabetes resulted some months after partial pancreatectomy when larger pieces of pancreas were left behind providing that the remaining pancreas was severed from its connection with the duodenum. This was presumably due to gradual atrophy and sclerosis of the remaining fragment.

Early histologic studies established that diabetes never occurred in the experimental animals in the presence of well-preserved islands of

Langerhans and that diabetes was never absent in the absence of islets.<sup>2a</sup> However, detailed microscopic observations on the islets of Langerhans contained in the remaining pancreatic tissue of animals rendered diabetic by subtotal pancreatectomy had to await the development of the special methods devised by Lane and Bensley for staining the specific granules of the islet cells. Such observations were finally forthcoming in 2 series of publications, 1 by F. M. Allen<sup>2</sup> and 1 by Homans.<sup>34</sup> Their first studies were carried out independently and published almost simultaneously in 1913.

Both of these investigators studied microscopically the remaining fragments of pancreatic tissue in dogs deprived of approximately nine-tenths of the pancreas, while Homans, in addition, made similar observations on cats deprived of about five-sixths of the pancreas. Partial pancreatectomy of this extent was usually followed in both species by the development of diabetes. Homans<sup>34b</sup> found significant changes in the remaining islands of Langerhans in partially pancreatectomized cats even when diabetes did not develop. In such animals within 5 days after operation, he noted diminution in the granule content of the islet cells. In cats and dogs rendered diabetic by partial pancreatectomy, both Homans<sup>34</sup> and Allen<sup>2a,2b</sup> observed progressive loss of the specific granules of the beta cells accompanied by swelling of these cells and the appearance of empty vacuoles in the cytoplasm which were devoid of any substance that could be fixed or stained. This last appearance was recognized at once as the counterpart of the hydropic degeneration of the islets of Langerhans in human diabetes previously described by Weichselbaum<sup>62</sup> and others. While these changes in the beta cells were progressing, the alpha cells remained practically normal with their full complement of granules. The nuclei and cell membranes of the beta cells remained normal in appearance even when the cytoplasm had been practically replaced by voluminous vacuoles, but eventually there followed rupture, disintegration and disappearance of the beta cells leaving the islets much reduced in size and composed only of the few remaining alpha cells. In addition to these alterations in the islets, Allen<sup>2b</sup> also observed in dogs the formation of numerous strands and clusters of duct cells with the appearance of vacuolation of these and of the epithelium of the smaller ducts in the end-stages of severe diabetes.

Allen<sup>2b</sup> found that the rapidity of development of the changes in the islets varied directly with the severity of the diabetes. With very severe unmitigated diabetes, the first positive vacuolation was found in from 4 to 7 days; maximum vacuolation was attained in about 1 month; and in 6 weeks to 2 months all beta cells had disappeared. Allen<sup>2b</sup> believed that the hydropic changes were probably reversible but he was unable to prove this conclusively. Later, however, when insulin became available, Copp and Barclay<sup>17</sup> demonstrated that the hydropic degeneration in dogs rendered diabetic by partial pancreatectomy could be reversed by the administration of insulin, but only for the duration of insulin therapy.

Regarding the pathogenesis of these islet lesions, both Homans<sup>34</sup> and Allen<sup>2a,2b</sup> argued that, since a small fraction of the pancreatic tissue was called upon to perform the work of the whole, it was reasonable to suppose that the changes in the islets of Langerhans were due to excessive functional demands. The succession of changes in the beta cells were interpreted as indicating excessive functional activity and exhaustion followed by hydropic degeneration and finally by disintegration of the beta cells. Both investigators pointed out the importance of their observations in

identifying the beta cells as the source of the pancreatic antidiabetic hormone. Their conclusions on these points, though entirely inferential, have stood through the intervening years without criticism until recently when Lukens and Dohan<sup>48c</sup> challenged the hypothesis of functional strain solely on the score of vagueness.

The nature of the stimulus to excessive function of the beta cells under the conditions of these experiments was an attractive problem which engaged Allen's attention especially. Both he and Homans had observed hydropic degeneration and disintegration of the beta cells only in association with diabetes. Allen<sup>2b</sup> had demonstrated that the severity of the lesions varied directly with the severity of the diabetes and that their development was promoted by a high carbohydrate diet. Allen's further investigations showed that the development of hydropic degeneration in the presence of diabetes was not dependent on hyperglycemia, glycosuria,<sup>2d</sup> lipemia or acidosis.<sup>2b</sup> He was able to induce the hydropic changes in fragments of pancreas separated from all nervous connections<sup>2c</sup> and failed to produce hydropic degeneration or any other alterations in the islets by interference with the circulation of the pancreas.<sup>2e</sup> In view of these findings, and especially the demonstration that the hydropic lesions were not dependent on hyperglycemia, Allen<sup>2d</sup> concluded that the humoral stimulus to excessive function of the beta cells "must be something deeper or more specific in connection with the diabetes." Although he could conceive of their internal secretion existing in the blood stream only in traces, he suggested that the islet cells may conceivably be sensitive to a deficiency of their own circulating hormone and that this deficiency provides the adequate stimulus. Allen regarded this idea as purely speculative, but no evidence to controvert his suggestion had appeared until recently when Lukens and Dohan,<sup>48c,49</sup> in their experiments on anterior pituitary diabetes in cats, made observations apparently contradictory to those of Allen which led them to favor hyperglycemia as the essential factor in the production of the typical lesions in the islets of Langerhans. More detailed reference to their experiments will be made presently.

**Anterior Pituitary Diabetes.** The not infrequent clinical association of diabetes with disorders of the pituitary gland had long been the only justification for the belief that the pituitary played an important rôle in the regulation of carbohydrate metabolism. However, in 1927, Johns, O'Mulvenny, Potts and Laughton<sup>41</sup> first recorded the occurrence of hyperglycemia, glycosuria and polyuria in dogs following injections of an extract of the anterior lobe of the pituitary. Houssay and Biasotti<sup>35</sup> in 1930 showed that diabetes produced in animals by pancreatectomy was ameliorated by hypophysectomy. Finally, in 1932, three groups of investigators almost simultaneously reported the production of diabetes in experimental animals by means of injections of extracts of the anterior lobe of the pituitary. These investigators were Evans, Meyer, Simpson and Reichert,<sup>26</sup> Baumann and Marine,<sup>9</sup> and Houssay, Biasotti and Rietti.<sup>36</sup> Although it was then established that a limited course of injections of anterior pituitary extract would produce a temporary or transient diabetic state which disappeared shortly after the injections ceased, Young<sup>64a</sup> in 1937 added materially to the knowledge of anterior pituitary diabetes by his observation that the daily injection in dogs of a suitable extract in large doses for a period of several weeks may produce permanent diabetes which persists indefinitely after cessation of the injections. However, the full significance of Young's observation was not realized until Richardson

and Young<sup>55b</sup> in 1938 first described lesions of the islets of Langerhans in association with anterior pituitary diabetes. The occurrence of such lesions in dogs has since been confirmed by a number of other investigators,<sup>14,19,20,61</sup> and the changes in the islets have been studied with special care by Richardson<sup>54</sup> and Ham and Haist.<sup>32</sup>

The lesions in the islands of Langerhans affect the beta cells almost exclusively. The alpha cells almost always remain normal with a normal content of granules, but varying degrees of depletion of alpha granules have been described in a few instances.<sup>32</sup> The changes in the beta cells correspond in every essential respect with those described by Homans<sup>34</sup> and Allen<sup>2a,2b</sup> in animals rendered diabetic by partial pancreatectomy. In dogs injected daily with anterior pituitary extract in suitable doses the beta cells exhibit progressive depletion of their specific granules which is usually almost complete at the end of 7 days. Toward the end of this period hydropic degeneration makes its appearance in the beta cells and progresses rapidly. There is a concomitant vacuolation or hydropic degeneration of the epithelium of the smaller pancreatic ducts and of the cords of undifferentiated epithelium. During this same early period mitotic figures may be found among the islet cells, and Ham and Haist<sup>32</sup> also observed mitotic activity in the cells of the small pancreatic ducts, in strands of undifferentiated epithelium and in acinar cells of the pancreas, as well as in other organs.

That the changes occurring within the first 7 days are completely reversible is evident from the studies of Ham and Haist<sup>32</sup> who observed recovery from hydropic degeneration of both islet and duct cells and restoration of about half of the normal complement of beta granules within 3 days after the last of 7 daily injections of anterior pituitary extract. Four days after the last injection granulation of the beta cells was complete and the islets restored to practically normal appearance. However, in 1 dog subjected to 7 daily injections and sacrificed 27 days thereafter, the islets of Langerhans exhibited slightly more collagen than usual in association with their vessels.

If daily injections of anterior pituitary extract be continued for 2 to 4 weeks or longer, diabetes persisting indefinitely after the cessation of the injections is the usual result. In the pancreatic tissue of dogs made permanently diabetic in this way, there is a scarcity of recognizable islets and evidence of disappearance of many beta cells with consequent reduction in size of the islands that remain. The latter may appear practically normal with ordinary stains,<sup>32</sup> but granule stains reveal that they are composed chiefly of alpha cells, sometimes with small numbers of agranular or hydropic beta cells. Although Richardson<sup>54</sup> regarded vacuolation of the smaller ducts of the pancreas as the most characteristic lesion following injections of anterior pituitary extracts, it is found only irregularly in permanently diabetic dogs.<sup>19,32</sup>

Ham and Haist<sup>32</sup> were particularly impressed by the close correlation between the extent of granulation of the beta cells in the different animals of their series and the insulin content of the respective pancreases as determined by Best, Campbell and Haist.<sup>10</sup>

Dohan, Fish and Lukens<sup>19</sup> found that atrophy of islets was not accompanied by fibrosis. On the other hand, Ham and Haist<sup>32</sup> described slight diffuse fibrosis of the pancreas and an increase of collagen about the blood-vessels of the islets. Richardson<sup>54,55b</sup> alone has described hyaline replacement of the beta cells in 3 dogs which had been diabetic for 5 months or longer. He thought it possibly significant that these animals had all had

a short period of insulin therapy which had been discontinued shortly before death. Two of the dogs also showed obstruction of the major ducts with acute pancreatitis. In view of recent demonstrations of the amyloid nature of the hyaline material found in the islets of Langerhans in some cases of human diabetes,<sup>1,3,28,59</sup> it is worth mentioning that the hyaline material described by Richardson<sup>54,55b</sup> gave the staining reactions of collagen while tests for amyloid material were negative.<sup>55b</sup>

Although dogs are evidently highly susceptible to the effects of anterior pituitary extracts, Young<sup>64b</sup> was unable to produce permanent diabetes by injections of such extracts in mice, rats, guinea pigs, rabbits or cats. Even during the course of the injections, mice, rats and guinea pigs showed practically no evidence of metabolic disturbance, while a minor proportion of the rabbits and cats exhibited only a slight and temporary glycosuria and ketonuria. Richardson and Young,<sup>55a</sup> however, were able to show by the use of a quantitative method of estimation of the volume of islet tissue, that in young rats treated daily for 2 weeks with a crude anterior lobe extract the amount of islet tissue was approximately doubled. Marks and Young<sup>50</sup> found that in such rats the insulin content of the pancreas was increased to nearly twice the normal value. More recently, Ogilvie<sup>53</sup> has shown that a similar increase in the volume of islet tissue occurs in rabbits subjected to daily injections of a crude saline extract of anterior pituitary gland. The increase in islet tissue was due to enlargement of the islets to about twice their original size, the number of islets remaining constant. Marks and Young<sup>50</sup> give reasons for believing that these effects are caused by an anterior pituitary pancreatropic factor which is not identical with either the diabetogenic or growth-promoting principle.

While intact cats are resistant to the effects of anterior pituitary extracts, Lukens and Dohan<sup>48a,c</sup> have succeeded in producing pituitary diabetes in cats previously deprived of one-half to three-fourths of the pancreas. The partial pancreatectomy was not of sufficient extent to produce diabetes of itself, but daily injections of anterior pituitary extract for several weeks produced diabetes of varying severity which persisted indefinitely after cessation of the injections. The changes in the islets of Langerhans were of the same character as in dogs, consisting of degranulation of the beta cells followed by hydropic degeneration. In the cat, however, hydropic degeneration persisted in a reversible state much longer than in the dog and was the characteristic finding during the first 3 months of diabetes, including the period of injections and the early period of permanent diabetes. Only after 3 or 4 months of diabetes were the islets found atrophic as compared with 3 to 4 weeks in dogs. They were then reduced in size and number and composed almost entirely of alpha cells with a few hydropic beta cells. Hyaline deposits and slight fibrosis were found in the islets of several cats observed for long periods. In several instances, too, the islets were infiltrated with lymphocytes and occasional neutrophils. Hyaline degeneration was frequently associated with interstitial pancreatitis as in Richardson's dogs.<sup>54</sup>

Campbell, Haist, Ham and Best<sup>15</sup> have shown in dogs that the concurrent administration of insulin hinders the development of hydropic degeneration in the islands of Langerhans which usually occurs during the period of injection of anterior pituitary extracts. In partially pancreatectomized cats, Lukens and Dohan<sup>48c,49</sup> found that suitable treatment within the first 3 months of diabetes resulted in restoration of the islets of Langerhans to a practically normal appearance and recovery of



the animals from diabetes, a recovery that was maintained after therapy was discontinued. Reduction in diet was found to be adequate treatment only if the diabetes was very mild, while treatment with insulin was effective regardless of the severity of the disease. Reduction of the blood sugar to normal by treatment with phlorhizin was equally effective.<sup>49</sup> When treatment by diet, insulin or phlorhizin was delayed until after 3 months of diabetes, that is, until the time when atrophy of the islands had occurred, recovery did not follow.

The pathogenesis of the lesions of the islets in anterior pituitary diabetes has been discussed in greatest detail by Ham and Haist.<sup>32</sup> Because of the very close resemblance of these lesions to those observed by Homans<sup>34</sup> and Allen<sup>2a,b</sup> in animals rendered diabetic by partial pancreatectomy, Ham and Haist, as well as Richardson,<sup>54</sup> were satisfied to regard the progressive degranulation and hydropic degeneration of the beta cells as having been caused by stimulation of these cells to excessive function. As to the cause of this stimulation, the arguments of Ham and Haist, which can scarcely be reproduced here, led to the conclusion that anterior pituitary extracts may act in two general ways to cause the beta cells to overwork: (1) by acting on tissues and organs other than the pancreas so as to increase the need for insulin, for example, by increasing the amount of carbohydrate to be metabolized and also by making insulin relatively ineffective; and (2) by exerting a trophic effect on the pancreas. The latter is indicated by mitotic activity in the islets and other epithelial elements of the pancreas and may be a factor in permitting the beta cells to secrete at a destructively high rate. In accordance with these conclusions, Ham and Haist thought that the early stages of diabetes produced by anterior pituitary extracts could be explained primarily by increased needs for insulin. The permanent diabetes persisting after the cessation of injections could be explained primarily as the result of diminished production of insulin owing to destruction of beta cells during the first stage.

As to the mechanism by which the beta cells may be stimulated to excessive function, Ham and Haist,<sup>32</sup> on the basis of several pieces of evidence, suggested that insulin secretion may be controlled by the blood insulin level and, therefore, that lowering of the level of insulin in the blood may impose an excessive functional strain upon the beta cells. This is essentially the same idea as that put forward by Allen<sup>2d</sup> long ago on the basis of his experiments with partially depancreatized dogs. In such animals treated with phlorhizin, Allen<sup>2d</sup> found that hydropic degeneration of the beta cells developed in spite of maintenance of the blood sugar at or below normal levels. This was one of the principal points of his evidence to show that hyperglycemia of itself was not responsible for the damage to the beta cells. Lukens, Dohan and Wolcott,<sup>48b,49</sup> however, in their recent studies of anterior pituitary diabetes in cats observed that lowering of the blood sugar level by means of phlorhizin for a period of 2 to 3 weeks led to recovery from diabetes and restoration of the islets to their normal state. This and other evidence adduced by them led Lukens, Dohan and Wolcott<sup>48c,49</sup> to suggest that hyperglycemia is the essential factor in the production of damage to the islets of Langerhans. They challenged the theory of functional "strain" on the beta cells largely because of its vagueness but submitted no alternative suggestion as to the mechanism involved.

**Alloxan Diabetes.** The most recently discovered form of experimental diabetes is that produced by alloxan. As long ago as 1937, Jacobs<sup>39</sup> noted

that the intravenous administration of alloxan in rabbits caused a transitory elevation of the blood sugar followed by profound hypoglycemia usually with death in convulsions in 7 to 10 hours unless this were averted by intravenous injections of glucose. Jacobs made no histologic examinations of the tissues and was unable to explain these effects. Some years later in 1943, Dunn, Sheehan and McLetchie,<sup>25</sup> apparently without knowledge of Jacobs' work, also gave intravenous injections of alloxan to rabbits with the aim of producing renal damage. The purpose of the experiments was frustrated by death of the animals within a day or two in a state of collapse with subnormal temperatures. It was observed that there was an initial rise of the blood sugar followed by an intense and fatal hypoglycemia. However, the most important contribution was their observation that these manifestations were accompanied by selective necrosis of the islets of Langerhans of the pancreas. None of the animals survived to exhibit signs of diabetes.

Very shortly afterwards, Brunschwig, Allen, Goldner and Gomori<sup>12</sup> observed several rabbits which survived injections of alloxan but exhibited only transitory hyperglycemia. They also reported hyperglycemia sustained for 2 or 3 weeks in 5 dogs following alloxan injection. Almost simultaneously, Bailey and Bailey<sup>5a</sup> reported that rabbits could be carried through the stage of hypoglycemia by repeated intravenous injections of dextrose with the subsequent establishment of a persistent diabetic state. A further report by Dunn and McLetchie<sup>24</sup> showed that subcutaneous injections of alloxan in rats could likewise produce necrosis of the islets of Langerhans and permanent diabetes. Goldner and Gomori<sup>30a</sup> subsequently described the production of necrosis of the islets and diabetes in dogs by means of a single intravenous injection of alloxan. These early observations were quickly confirmed by a number of other investigators in different parts of the world. The studies of the effects of alloxan have since been extended to several other species of animals and numerous investigations have been directed toward elucidation of the mechanisms involved.

Gomori and Goldner<sup>31a</sup> in their paper on alloxan diabetes in white rats, reported their failure to produce the same effects in hooded rats given intraperitoneal injections of alloxan. Accordingly, they regarded hooded rats as being resistant. However, Duff and Starr<sup>21a</sup> were successful in producing necrosis of the islets and persistent diabetes in hooded rats by single subcutaneous injections of alloxan in a slightly larger dose. Goldner and Gomori<sup>30a</sup> tried the effects of alloxan in guinea pigs, cats and pigeons, as well as in rats, rabbits and dogs and found all of these species to be sensitive in various degrees to alloxan. Diabetes has not been observed in guinea pigs since lesions of the islets are found only in the animals that die within 24 hours after injection of alloxan.<sup>29</sup> In pigeons, alloxan causes a disturbance not only of carbohydrate but of uric acid metabolism.<sup>30d</sup> Mirsky<sup>52</sup> has recently shown that alloxan injection in the duck, while it causes necrosis of the islets of Langerhans, is as ineffective as surgical pancreatectomy in producing diabetes in this species. Banerjee<sup>8</sup> first produced alloxan diabetes in rhesus monkeys and this observation has been confirmed,<sup>29</sup> but human subjects tolerate repeated relatively massive, intravenous doses of alloxan without the development of diabetes and without significant histologic changes in the islets of Langerhans.<sup>11,13</sup> Friedgood and Miller<sup>27</sup> have demonstrated that alloxan injected intravenously in pregnant rats passes rapidly through the placenta and appears in the fetal blood stream. While diabetes developed in pregnant rats

injected shortly before parturition, the offspring showed no signs of diabetes and their pancreatic islets presented no definite pathologic change.

Alloxan, the ureide of mesoxalic acid, is a colorless powder easily soluble in water or alcohol. It is administered in 2 to 5% aqueous solution intravenously, intraperitoneally, or subcutaneously. The last 2 routes are the least satisfactory because alloxan solution is distinctly acid and cannot be neutralized without inactivation of the alloxan.<sup>29</sup> Moreover, alloxan is rapidly destroyed in the body, and in rabbits subcutaneous or intraperitoneal injections are ineffective,<sup>43</sup> though effective in rats.<sup>6,21a,24,31a</sup> A single injection is sufficient to produce the desired results, although divided doses at short intervals have frequently been successfully employed. Alloxan is capable of injuring the renal tubular epithelium as well as the islets of Langerhans and if the diabetogenic dose is much exceeded the animal dies in a few days of uremia superimposed on diabetes. Still larger doses cause a toxic death in a few hours. As Goldner<sup>29</sup> has pointed out, the margin between the diabetogenic, uremic and fatal dose is widest in the rabbit, rat and dog, narrower in the monkey and smallest in the cat, guinea pig and pigeon. Different species vary in their sensitivity to alloxan and individual variations between members of the same species are considerable. An animal that has proved refractory to a first dose of alloxan seldom responds to subsequent doses.<sup>21b,30a,33,43</sup> Among the various species tested the greatest sensitivity is found in the dog, in which the diabetogenic single dose of alloxan is 50 to 100 mg. per kg. of body weight intravenously.<sup>29</sup> Other species in order of decreasing sensitivity, with the diabetogenic doses of alloxan, are as follows: monkey (100 to 150 mg./kg. I.V.), cat (150 mg./kg. I.V.), pigeon (125 to 200 mg./kg. I.V.), rabbit (100 to 200 mg./kg. I.V.), and rat (including hooded) (200 to 300 mg./kg. subcutaneously or intraperitoneally).<sup>29</sup> Human beings tolerate doses of 600 to 1000 mg. of alloxan per kg. of body weight intravenously without the development of diabetes and without histologic effects on the islets of Langerhans.<sup>11,43</sup>

In their first report on the effects of alloxan, Dunn and his co-workers<sup>25</sup> mentioned that a quinoline compound, Styryl-Quinoline No. 90, had effects like those of alloxan when injected into rabbits. Jacobs,<sup>39</sup> Thorogood,<sup>58</sup> and Goldner and Gomori<sup>30c</sup> tested in animals a variety of chemicals related to alloxan and the latter investigators also tried quinoline compounds and various oxidizing substances, but no effects similar to those of alloxan were observed. Although alloxantin was among the chemicals tested with negative results,<sup>30c,39</sup> Koref, Vargas, Rodriguez and Telchi<sup>45</sup> later reported the production of necrosis of the islets of Langerhans and diabetes in rabbits injected with alloxantin. Their observations have been confirmed by Bailey and Bailey.<sup>5b</sup> Weinglass, Frame and Williams<sup>63</sup> have recently demonstrated inhibition of the diabetogenic action of alloxan by the intravenous injection of several substances that combine chemically with alloxan or inhibit some of its chemical actions. These were ineffective when injected more than 5 minutes before or after alloxan.

The histologic changes in the islets of Langerhans following a single injection of alloxan, as described by various investigators, appear to be practically identical in rabbits<sup>5a,7,11,22,23,25,30b,33</sup> and in rats.<sup>6,21a,24,31a,38,45</sup> In both species, even as early as 5 minutes after the injection of a diabetogenic dose of alloxan, slight but definite changes are discernible in the nuclei and cytoplasm of the beta cells with a suggestion of some diminution of their specific granules.<sup>7,38</sup> At from 10 to 15 minutes after injection there is a definite reduction of granules.<sup>7,38</sup> These changes affect first the beta

cells at the centers of the larger islets.<sup>7,38</sup> Before the end of 1 hour there is some shrinkage of the affected cells which appear more closely packed<sup>7</sup> and there is a corresponding widening of the pericapillary spaces.<sup>38</sup> By the end of 1 to 2 hours definite pyknosis of nuclei is evident<sup>7,11,21a,22</sup> and this becomes progressively more conspicuous and extensive in the next few hours. At the end of 3 hours some of the affected cells may be detached from one another and rounded in shape with homogeneous, eosinophilic cytoplasm.<sup>7,21a,22</sup> In the ensuing hours the cytoplasm may become further shrunken<sup>7,22,31a</sup> or may show conspicuous swelling.<sup>21a</sup> Signs of disintegration of the cytoplasm with coalescence of the most affected cells begin to appear. While shrunken, pyknotic nuclei may remain visible for 16 to 24 hours or more, increasing numbers of nuclei begin to show karyolysis and there is evidence of complete disintegration and disappearance of individual cells from 5 hours onward.<sup>7</sup> These changes continue, until at the end of 20 to 24 hours the centers of the islets are occupied only by pale staining granular debris in which the shadows of nuclei and occasional necrotic cells can barely be recognized.<sup>7,21a,23,24,25,31a</sup> The time of final disappearance of the specific granules of the beta cells is variously reported at from 15 minutes<sup>38</sup> to 2 or 3 days.<sup>31a</sup>

Following small single doses of alloxan, the changes in the islets are of the same kind as described above, but of less severe degree.<sup>22</sup> On the other hand, after massive single doses of 700 mg./kg. subcutaneously in hooded rats, Duff and Starr<sup>21b</sup> found the changes leading to necrosis were greatly accelerated. The state of the islets at the end of 8 to 10 hours was comparable with that just described at the end of 24 hours after the injection of the customary diabetogenic dose of alloxan.

While the changes described are proceeding in the beta cells, the peripherally placed alpha cells remain for the most part undamaged though they may show some swelling and evidence of slight degenerative change.<sup>22</sup> Accordingly, many of the islets show a necrotic center surrounded by a layer of surviving alpha cells. Some of the alpha cells, however, may suffer greater injury leading to necrosis of single cells here and there.<sup>21a,22,23,38</sup> According to some descriptions, all of the cells of both alpha and beta types are apparently destroyed in practically all of the islets.<sup>5a,6,7</sup>

The extent of the damage in the initial stages seems to determine what may be observed later. In any case the necrotic debris is rapidly removed so that no trace of it is left after 3 to 5 days and there is a corresponding collapse of the islet structure. When destruction of islet tissue has been extensive there is frequently recorded at the end of 5 days or more after injection the impression of great scarcity of islets in the pancreatic tissue<sup>6,7,11,21a,23,24,25</sup> even though small islets may be identified here and there on closer examination. In both rabbits and rats after more prolonged periods there are recorded instances in which it was impossible to find any islet tissue at all.<sup>6,24,38</sup> On the other hand, a peripheral layer of alpha cells is frequently spared and even a few of the beta cells may escape destruction. In this event, when the debris of necrotic cells has disappeared, the islets may be found in normal numbers and even of normal appearance when examined with ordinary stains, though they are frequently reduced in size. However, stains for specific granules show that the islets consist either of alpha cells exclusively or of alpha cells with a few non-granular cells of indifferent type.<sup>7,21a,31a,33</sup> It has been suggested that the alpha cells actually increase in number,<sup>7,30b,31a</sup> but mitotic figures have been only rarely observed amongst the surviving cells.<sup>22,24,31a</sup> Hydropic changes in beta cells have never been observed during the early

development of the lesions described and, indeed, such changes have been reported in only 2 instances in rabbits rendered diabetic by alloxan and examined after 48 and 58 days respectively.<sup>43</sup> The hydropic degeneration in these animals was attributed by the authors to the effect of hyperglycemia on beta cells that had escaped destruction by alloxan.

Although the production of alloxan diabetes in dogs has been reported by several investigators,<sup>11,12,16,30a</sup> the histologic changes in the pancreas have been described in detail only by Brunschwig and Allen<sup>11</sup> and Goldner and Gomori.<sup>30a</sup> The changes that they observed in the islets of Langerhans are similar to those described in rats and rabbits. The alpha cells remain well preserved and numerous while the beta cells are mostly destroyed, and those that remain show loss of granules by the 3rd day.<sup>30a</sup> The islets become somewhat shrunken and less conspicuous than normal and consist of well-preserved alpha cells possibly in increased numbers together with a few beta cells lacking in granules, or small non-granular cells of unidentifiable type. Goldner and Gomori<sup>30a</sup> also observed extreme vacuolation or hydropic degeneration of the epithelium of the intralobular pancreatic ducts in dogs rendered diabetic by alloxan and examined at 16 to 18 days. In other animal species<sup>8,29,30d,52</sup> the effects of alloxan on the islets of Langerhans appear to be essentially the same as in rats, rabbits and dogs, though the histologic changes have not been described nearly so carefully. It seems clear that in all species the beta cells bear the brunt of the injury and that the alpha cells, if they are injured at all, are the last to be destroyed.

The effects of repeated small doses of alloxan have been studied by several investigators. In 2 rabbits given daily intravenous injections of alloxan in doses of 40 mg./kg., Bailey and co-workers<sup>6,7</sup> observed the development of diabetes after the 7th and 13th injections respectively. The animals were then sacrificed for histologic examination which revealed unique lesions of the islets of Langerhans. Some of the islet cells, especially those at the periphery, appeared essentially normal. In other cells the nucleus and the ground substance of the cytoplasm were well preserved, but no granules were present. Numerous cells presented the typical appearance of hydropic degeneration and a few of these showed irreversible nuclear changes. Mitotic figures were seen in several islet cells but in no case was there more than one mitosis in a single islet. As the authors commented,<sup>6</sup> "This complex picture of normal cells, slightly injured cells, cells with hydropic degeneration, irreversibly damaged cells and a mitosis in a single islet is not clearly duplicated in any other form of experimental diabetes or in human patients."

Hughes and Hughes<sup>37</sup> gave rats daily subcutaneous injections of alloxan in doses ranging from 1 to 125 mg./kg. With the latter dose after periods of treatment of 2 weeks to 2 months, degenerative changes were found in the beta cells of the islets of Langerhans, consisting of various degrees of degranulation of the cytoplasm and pyknosis of nuclei. With daily doses of 25 mg./kg. or less, there was little sign of damage to the islet cells until the end of 2 months. Measurements of the diameters of the beta cells in islets of different sizes in normal and treated animals, together with observations of the distribution of beta cells injured by alloxan, led to the conclusion that there is in the normal pancreas a cycle of maturation and enlargement of the islets followed by involution and cell shrinkage. Alloxan in the low dosage employed caused destruction of the older beta cells only, which in the normal pancreas, are found in the largest islets.

Duff and Starr<sup>21b</sup> tried the effects of repeated doses of alloxan in hooded

rats. Subcutaneous doses of 50 and 75 mg./kg. repeated daily for periods up to 80 days produced no effect on the blood sugar level nor any evident histologic alteration in the islets of Langerhans. Following daily doses of 100 mg./kg. in several animals the blood sugar rose on the 4th day to a level in the neighborhood of 200 mg. % and so remained for several days. The blood sugar then fell to 150 mg. %, and never rose again above that level. Such doses of alloxan were continued for periods up to 50 days, but histologic examination of the pancreas revealed only slight pyknosis of nuclei in the central cells of some of the larger islets. There was no sign of fibrosis or hyalinization such as is found in some human cases of diabetes.<sup>61</sup>

Almost all authors who have described the pancreas following alloxan injections in the various species studied have noted at every stage a complete lack of cellular inflammatory reaction, either in relation to the necrotic islets or in the remainder of the pancreatic tissue. Apart from the vacuolation of intralobular pancreatic ducts described in dogs by Goldner and Gomori,<sup>30a</sup> all agree that the duct and acinar tissue of the pancreas in all species is maintained in essentially normal state. However, Duff and Starr<sup>21a</sup> observed in hooded rats a very striking increase in mitotic figures in the acinar cells of the pancreas beginning at 2 hours after injection of alloxan and reaching a peak at 17 hours. Thereafter the number of mitotic figures decreased to approximately normal rarity by the end of 24 hours. The significance of this observation is not apparent.

Apart from the pathologic changes in the pancreas, alloxan in diabetogenic doses causes no very striking lesion except in the kidneys, where degrees of damage varying from slight degenerative change to necrosis of the epithelium of the convoluted tubules are frequently mentioned.<sup>6,7,11,21a,23,24,25,30a</sup> Extreme fatty infiltration of the liver is found in dogs after alloxan injection<sup>30a</sup> but in other animals fatty changes in the liver are minimal or absent.<sup>6,7,21a,24,31a,33</sup> The pituitary, thyroid and parathyroid glands, when mentioned, have invariably been described as essentially normal.<sup>7,21a,23,24</sup> The adrenal glands are usually described either as normal or as showing slight and variable histologic changes duplicated in control animals or interpreted as having no significance by those who observed them.<sup>6,7,21a,23,24,30a</sup> However, Hard and Carr<sup>33</sup> suggested that importance may be attached to their finding of areas of fragmentation and shrinkage of cells of the adrenal medulla seen shortly after the injection of alloxan. Kennedy and Lukens<sup>43</sup> found that a diabetogenic dose of alloxan causes hemolysis in rabbits and a rapid fall of the red blood cell count to 1 or 2 million but the count returns to normal in about 3 weeks.

In animals rendered diabetic by alloxan, the glycogen content of the liver has been reported to be within normal limits,<sup>33</sup> but more frequently is reduced in amount.<sup>21a,30a,31a,46</sup> Histologic studies failed to reveal an increase of glycogen in the heart muscle of diabetic rats,<sup>21a</sup> but Lackey *et al.*<sup>46</sup> found by chemical analysis a significant increase in the glycogen content of the heart muscle and a decrease in that of skeletal muscle. If glycosuria has been present, glycogen may be demonstrated in the tubular epithelium of the kidney, especially that of Henle's loops.<sup>21a,29,30a,31a</sup>

Although the clinical course of alloxan diabetes differs somewhat in different animal species,<sup>29</sup> the classical signs of diabetes mellitus, hyperglycemia, glycosuria, polyuria, polydipsia, polyphagia, loss of weight, hyperlipemia, ketonuria, acidosis and coma have all been observed repeatedly by different investigators. In addition, there is an unusual susceptibility

to infections, especially in dogs.<sup>29</sup> Even more important is the observation of Bailey *et al.* in Boston of the development of cataracts in 5 rabbits beginning 4 to 6 weeks after induction of diabetes<sup>6,7</sup> and in 2 diabetic rats kept alive for 4 months after injection of alloxan.<sup>6</sup> Cataracts seemed to develop more quickly and to progress further in rabbits with poorly controlled diabetes than in those receiving insulin.<sup>7</sup> It appears to be questionable whether the development of cataracts is solely dependent on the diabetic state for they have not been observed in association with protracted alloxan diabetes in any animal species by other groups of investigators in Philadelphia,<sup>43</sup> Chicago<sup>29,30,31</sup> and Montreal.<sup>21</sup> Arteriosclerosis has been sought, but not found, in association with alloxan diabetes; it has not been seen even in rabbits<sup>7,21b</sup> in which the arterial system is notoriously sensitive to injury.

Everything that has been said up to this point has had reference to the effects of alloxan in intact animals, but its effects have also been studied in animals subjected to adrenalectomy or hypophysectomy. In previously adrenalectomized or hypophysectomized hooded rats, Duff and Starr<sup>21b</sup> found that the lesions of the islets of Langerhans following alloxan injection develop in a manner quite indistinguishable from that in intact animals.<sup>21a</sup> Bailey<sup>4</sup> made the same observation in rats previously subjected to hypophysectomy. It seems clear, therefore, that the destructive effects of alloxan on the beta cells of the islets are not mediated through effects upon either the adrenal or pituitary glands.

The influence of adrenalectomy and of hypophysectomy on the characteristic initial fluctuations of the blood sugar level following alloxan injection and on the ensuing diabetes have also been studied by several investigators whose observations may be summarized briefly.

It has been demonstrated by Goldner and Gomori<sup>30c</sup> in rabbits, by Kirschbaum, Wells and Molander<sup>44</sup> in rats, and by Duff and Starr<sup>21b</sup> in hooded rats, that the immediate hyperglycemia following characteristically within the first few hours after injection of diabetogenic doses of alloxan is practically abolished by bilateral adrenalectomy. All of these investigators found also that the phase of hypoglycemia occurred earlier and was more profound than in intact animals. All adrenalectomized animals exhibited hypoglycemic convulsions, even though in the case of the rats, hypoglycemic convulsions were never observed in intact animals given identical doses of alloxan.<sup>21a,44</sup> Goldner and Gomori<sup>30c</sup> obtained the same effects in 3 rabbits by destruction of the adrenal medulla alone, but this observation was not confirmed by Kirschbaum *et al.*<sup>44</sup> who found that the presence of regenerated adrenal cortical tissue following adrenal enucleation in 3 rats was sufficient to prevent the occurrence of hypoglycemia. Janes and Friedgood<sup>40</sup> have recently demonstrated that adrenalectomy in rats previously rendered diabetic by alloxan is followed by a marked reduction or complete disappearance of diabetic symptoms, a response similar to that shown by pancreatectomized animals.

Kirschbaum *et al.*<sup>44</sup> found that injection of alloxan in previously hypophysectomized rats produced an initial blood sugar curve similar to that observed in adrenalectomized animals. The usual immediate hyperglycemic reaction was lacking and there was early appearance of profound hypoglycemia and convulsions within 6 hours after injection. The observations were not carried beyond this time. Although it is not so stated, it appears probable that these animals were starved for some hours before injection of alloxan and perhaps throughout the experiments. Duff and Starr,<sup>21b</sup> in hitherto unpublished experiments in hooded rats,

found that if hypophysectomized animals were allowed food *ad lib.* before and after injection of alloxan, the subcutaneous injection of a diabetogenic dose was regularly followed by an immediate and rapid rise of blood sugar within the first 2 hours to levels slightly higher on the average than those observed in intact animals.<sup>21a</sup> This was followed by a precipitous fall of the blood sugar to hypoglycemic levels. This fall continued more gradually until hypoglycemic convulsions occurred in the majority of the animals at from 8 to 18 hours after injection. Some of the animals died in convulsions but others, with or without convulsions, survived and were sacrificed for histologic examination at intervals up to 5 days. Although histologic studies showed destruction of the islets of Langerhans quite as extensive as in intact animals,<sup>21a</sup> there was no evidence of diabetes during the periods of survival. The blood sugar remained at more or less normal levels, but there were irregular fluctuations somewhat above and below the normal limits. The suppression of diabetes in these experiments is comparable with the beneficial effect of hypophysectomy in animals rendered diabetic by pancreatectomy as first observed by Houssay and Biasotti.<sup>35</sup>

The mechanism by which alloxan causes the characteristic initial fluctuations of the blood sugar level and necrosis of the islets of Langerhans has been the subject of numerous investigations. Jacobs,<sup>39</sup> who was unaware of its destructive effects on the islets, compared the hypoglycemic action of alloxan with that of insulin. It has since been shown that alloxan does not exert a hypoglycemic effect in depancreatized dogs<sup>30c,56</sup> nor in animals previously made diabetic with alloxan.<sup>30c,43,56</sup> Thus, it is clear that absence of intact islets of Langerhans robs alloxan of its ability to produce hypoglycemia. Alloxan does not inhibit the effect of insulin when they are injected simultaneously,<sup>30b,c</sup> nor is insulin inactivated by alloxan *in vitro*.<sup>30b,c,43</sup> Corkill, Fantl and Nelson<sup>18</sup> have demonstrated in the spinal eviscerated cat that alloxan *per se* has no effect on the utilization of glucose nor on the blood sugar level.

Dunn and his collaborators,<sup>25</sup> on their discovery of the fact that alloxan causes necrosis of the islets of Langerhans, were impressed by the selective character of this injurious effect and thought that it was best explained on the basis of a disturbance involving their special function. They, therefore, suggested the possibility that alloxan produced a mobilization of carbohydrate, causing the initial hyperglycemia, to which the cells of the islets reacted by an excessive outpouring of insulin. This would account for the rapid fall of blood sugar which ushers in the hypoglycemic phase of the reaction. Moreover, it was suggested that the necrosis of the islet cells which occurred during the same period could be explained by this overstimulation of the cells to the point of destructive functional activity. This interesting hypothesis was later disproved by several experimental observations. Goldner and Gomori<sup>30b,c</sup> demonstrated that prevention of the initial hyperglycemia by insulin and of the ensuing hypoglycemia by glucose injections does not prevent destruction of the beta cells nor the ultimate appearance of diabetes. The initial hyperglycemia following alloxan injection is also prevented by adrenalectomy, but this does not protect the islets from necrosis.<sup>21b</sup> Moreover, the histologic studies outlined in preceding paragraphs show that degenerative changes appear in the beta cells within 5 minutes after the injection of alloxan and that these changes have progressed to necrosis of many of the cells by the time hypoglycemia makes its appearance. These facts are scarcely consistent with the idea of necrosis caused by exhaustion from excessive secretion of insulin.



Bailey and Bailey<sup>5a</sup> suggested that the immediate hyperglycemia following injection of alloxan was a non-specific effect and that the hypoglycemic phase might be due simply to the escape of a large amount of insulin from the dying islet cells. Hughes, Ware and Young<sup>38</sup> proposed the same hypothesis with the additional suggestion that the initial hyperglycemia was caused by a release of adrenalin. They added support to this idea by showing in the rabbit that the typical blood sugar curve observed during the first 8 hours after injection of alloxan could be duplicated by the injection of adrenalin and of a quantity of insulin equal to that contained in the pancreas of a normal rabbit. If this hypothesis is correct, bio-assay of the insulin content of the pancreas at intervals after alloxan injection should reveal a profound decrease of insulin content during the acute phase of the reaction, the decrease beginning *after* necrosis of islet cells has begun to occur. This is precisely the observation recorded by Ridout, Ham and Wrenshall<sup>56</sup> in a study of this kind carried out in rats and dogs. Not only is this observation in accord with the theory outlined above, but so also are all of the data on the effects of alloxan accumulated up to the present time and summarized in the preceding pages of this review.

Of course, it is implicit in the hypothesis proposed by Hughes, Ware and Young<sup>38</sup> that the cells of the islets of Langerhans are killed by a direct selective action of alloxan upon them, and there is evidence that the injury is inflicted in a very short space of time, not exceeding 5 minutes after injection. Alloxan is inactivated by neutralization<sup>29</sup> and it seems obvious that neutralization by buffers of the body fluids would occur very shortly after injection.<sup>31b</sup> Leech and Bailey,<sup>47</sup> employing a quantitative chemical method devised by them for the determination of alloxan in blood, have demonstrated in rabbits that injected alloxan disappears almost completely from the blood within 2 minutes. Substances that inhibit the diabetogenic action of alloxan are ineffective when injected more than 5 minutes after alloxan.<sup>63</sup> Gomori and Goldner<sup>31b</sup> have shown that interruption of the blood supply to a portion of the dog's pancreas during and for a period of 1 to 6 minutes after injection of alloxan, will protect the islets in that part of the pancreas from alloxan damage. Thus the injury produced by alloxan is known to be very acute and all evidence points to a direct action of this chemical upon the islet cells, but the reason for the high susceptibility of the beta cells to damage by alloxan and the means by which it exerts its cytotoxic effect remain obscure.

Alloxan diabetes, when it is established, is evidently caused by a relative or absolute deficiency of insulin production owing to destruction of the beta cells of the islets. This concept is supported not only by logic and by metabolic studies,<sup>29,43</sup> but by the direct observation of Goldner and Gomori<sup>30c</sup> that the insulin content of the pancreas of dogs made diabetic by alloxan is reduced to about one-fourth of the normal value.

**Comment.** Between the surgical diabetes produced by partial pancreatectomy and the endocrine diabetes produced by anterior pituitary extracts, there are many similarities and relatively few differences. Both of them, however, differ in several important respects from the chemical diabetes produced by alloxan, as Goldner<sup>29</sup> has pointed out. In all 3 forms of the experimental disease, the final permanent phase of the diabetes is caused primarily by a deficiency of insulin occasioned by loss of the beta cells of the islets of Langerhans, but the stages leading up to this deficiency differ considerably.

The hydropic degeneration of the beta cells produced by partial pan-

createctomy appears to be identical with that produced by anterior pituitary extracts. This change is at first reversible and only later progresses to irreversible cell damage. In both instances hydropic degeneration is probably caused by the excessive functional demands associated with hyperglycemia. Consequent upon this demand there is excessive secretory activity and "overstrain" of the cells. The hydropic changes in the beta cells can be promoted by increasing the strain through the use of a high carbohydrate diet; they can be prevented or reversed in the early stages by relieving the strain through dietary restriction or treatment with insulin in the case of surgical diabetes, or, in the case of anterior pituitary diabetes, by stopping the injections of anterior pituitary extract or by treatment with restricted diet, insulin or phlorhizin. In both types of experimental diabetes an initial elevation of the blood sugar appears to be essential to the production of permanent diabetes and the rate of progression of the cellular changes in the pancreatic islets is roughly proportional to the degree of hyperglycemia. In all of these respects, these 2 forms of experimental diabetes differ from alloxan diabetes.

In alloxan diabetes, the beta cells of the islets show, from the beginning, degenerative changes that lead quickly to necrosis without the appearance of a stage in any way resembling hydropic degeneration. The necrosis is probably caused by the direct action of alloxan on the islet cells and this injury is irreversible. Necrosis of beta cells follows a diabetogenic dose of alloxan regardless of the carbohydrate content of the diet or the absence of food.<sup>21b</sup> Prevention of the initial hyperglycemia by treatment with insulin or phlorhizin does not prevent necrosis of the islets of Langerhans nor the subsequent appearance of diabetes; nor does such treatment permanently improve the diabetes once established.<sup>30b,c</sup>

Surgical diabetes can be produced in certain animals (*e. g.*, dogs and cats) by a single operation requiring no great technical skill. Endocrine diabetes is brought about by repeated injections of anterior pituitary extract continued over a period of days or weeks. Chemical diabetes, on the other hand, can be produced within a space of 24 hours by a single injection of alloxan. Moreover, alloxan is effective in small laboratory animals such as rats and rabbits which are refractory to the diabetogenic effects of anterior pituitary extract. In these species, too, the production of diabetes by pancreatectomy is scarcely feasible for large scale research because of the technical difficulty of excising a sufficiently large proportion of the pancreatic tissue and the consequent uncertainty of the results. It is obvious, therefore, that the discovery of the diabetogenic property of alloxan has placed in the hands of investigators an invaluable new tool for the prosecution of further research in the field of diabetes.

The various methods available for the experimental production of diabetes in animals have not been conspicuously successful in reproducing lesions of the islets of Langerhans similar to those encountered amongst human cases of diabetes mellitus.<sup>61</sup> The hydropic degeneration of the beta cells observed in animals with surgical or endocrine diabetes does, however, appear to be an exact replica of the hydropic changes seen in certain human cases. Hydropic degeneration of the beta cells in cases of diabetes in man is far from common;<sup>61</sup> but it seems reasonable, on the basis of the experimental observations, to interpret such changes, when observed, as evidence of functional overstrain. The fibrosis and hyalinization of the islets seen in a few animals after prolonged anterior pituitary diabetes are suggestively like the alterations observed in some human cases of diabetes.<sup>61</sup> However, such changes seem to occur only irregu-

larly in the experimental animals and the significance of these lesions in human diabetes is open to question because of their not infrequent occurrence in non-diabetic subjects.<sup>1,3,61</sup>

Dunn and his collaborators<sup>23,25</sup> suggested the possibility that alloxan might be of importance in the causation of human diabetes. The early changes in the islets produced by alloxan do not resemble any lesion commonly observed in human diabetes,<sup>61</sup> but Dunn *et al.*<sup>23</sup> were able to discover in the literature reports of 4 or 5 human cases in which necrosis of the islets was described. It seems, however, most improbable at present that alloxan plays a rôle in the etiology of human diabetes for several reasons. There is little, if any, evidence that alloxan has any part in physiologic processes in spite of its close relation to uric acid.<sup>29</sup> It is very rapidly destroyed when injected into animals.<sup>31b,47</sup> Moreover, the high resistance of human subjects to the diabetogenic effects of alloxan has already been established.<sup>11,13</sup>

#### REFERENCES

- (1.) Ahronheim, J. H.: *Am. J. Path.*, 19, 873, 1943. (2.) Allen, F. M.: (a) *Studies Concerning Glycosuria and Diabetes*, Cambridge, Mass, Harvard Univ. Press, Chapters 10, 21, 22, 1913; (b-c) *J. Metab. Res.*, 1, 5, 53, 75, 89, 1922. (3.) Arey, J. B.: *Arch. Path.*, 36, 32, 1943. (4.) Bailey, C. C.: Personal communication cited by Joslin.<sup>42</sup> (5.) Bailey, C. C., and Bailey, O. T.: (a) *J. Am. Med. Assn.*, 122, 1165, 1943; (b) Personal communication cited by Joslin.<sup>42</sup> (6.) Bailey, C. C., Bailey, O. T., and Leech, R. S.: *New England J. Med.*, 230, 533, 1944. (7.) Bailey, O. T., Bailey, C. C., and Hagan, W. H.: *Am. J. Med. Sci.*, 208, 450, 1944. (8.) Banerjee, S.: *Lancet*, 2, 658, 1944. (9.) Baumann, E. J., and Marine, D.: *Proc. Soc. Exp. Biol. and Med.*, 29, 1220, 1931-32. (10.) Best, C. H., Campbell, J., and Haist, R. E.: *J. Physiol.*, 97, 200, 1939-40. (11.) Brunschwig, A., and Allen, J. G.: *Cancer Res.*, 4, 45, 1944. (12.) Brunschwig, A., Allen, J. G., Goldner, M. G., and Gomori, G.: *J. Am. Med. Assn.*, 122, 966, 1943. (13.) Brunschwig, A., Allen, J. G., Owens, F. M., and Thornton, T. F.: *J. Am. Med. Assn.*, 124, 212, 1944. (14.) Campbell, J., and Best, C. H.: *Lancet*, 1, 1444, 1938. (15.) Campbell, J., Haist, R. E., Ham, A. W., and Best, C. H.: *Am. J. Physiol.*, 129, 328, 1940. (16.) Carrasco-Formiguera, R.: *J. Lab. and Clin. Med.*, 29, 510, 1944. (17.) Copp, E. F. F., and Barclay, A. J.: *J. Metab. Res.*, 4, 445, 1923. (18.) Corkill, A. B., Fantl, P., and Nelson, J. F.: *Med. J. Australia*, 1, 285, 1944. (19.) Dohan, F. C., Fish, C. A., and Lukens, F. D. W.: *Endocrinology*, 28, 341b, 1941. (20.) Dohan, F. C., and Lukens, F. D. W.: *Am. J. Physiol.*, 125, 188, 1939. (21.) Duff, G. L., and Starr, H.: (a) *Proc. Soc. Exp. Biol. and Med.*, 57, 280, 1944; (b) Unpublished observations. (22.) Dunn, J. S., Duffy, E., Gilmour, M. K., Kirkpatrick, J., and McLetchie, N. G. B.: *J. Physiol.*, 103, 233, 1944. (23.) Dunn, J. S., Kirkpatrick, J., McLetchie, N. G. B., and Telfer, S. V.: *J. Path. and Bact.*, 55, 245, 1943. (24.) Dunn, J. S., and McLetchie, N. G. B.: *Lancet*, 2, 384, 1943. (25.) Dunn, J. S., Sheehan, H. L., and McLetchie, N. G. B.: *Lancet*, 1, 484, 1943. (26.) Evans, H. M., Meyer, K., Simpson, M. E., and Reichert, F. L.: *Proc. Soc. Exp. Biol. and Med.*, 29, 857, 1931-32. (27.) Friedgood, C. E., and Miller, A. A.: *Proc. Soc. Exp. Biol. and Med.*, 59, 61, 1945. (28.) Gellerstedt, N.: *Beitr. z. path. Anat. u. allg. Path.*, 101, 1, 1938. (29.) Goldner, M. G.: *Bull. New York Acad. Med.*, 21, 44, 1945. (30.) Goldner, M. G., and Gomori, G.: (a) *Endocrinology*, 33, 297, 1943; (b) *Proc. Soc. Exp. Biol. and Med.*, 55, 73, 1944; (c) *Endocrinology*, 35, 241, 1944; (d) *Proc. Soc. Exp. Biol. and Med.*, 58, 31, 1945. (31.) Gomori, G., and Goldner, M. G.: (a) *Proc. Soc. Exp. Biol. and Med.*, 54, 287, 1943; (b) *Proc. Soc. Exp. Biol. and Med.*, 58, 232, 1945. (32.) Ham, A. W., and Haist, R. E.: *Am. J. Path.*, 17, 787, 1941. (33.) Hard, W. L., and Carr, C. J.: *Proc. Soc. Exp. Biol. and Med.*, 55, 214, 1944. (34.) Homans, J.: (a) *Proc. Roy. Soc. London, Ser. B*, 86, 73, 1913; (b) *J. Med. Res.*, 30, 49, 1914; (c) *J. Med. Res.*, 33, 1, 1915. (35.) Houssay, B. A., and Biasotti, A.: (a) *Compt. rend. Soc. de biol.*, 104, 407, 1930; (b, c) 105, 121, 124, 1930. (36.) Houssay, B. A., Biasotti, A., and Rietti, C. T.: *Compt. rend. Soc. de biol.*, 111, 479, 1932. (37.) Hughes, H., and Hughes, G. E.: *Brit. J. Exp. Path.*, 25, 126, 1944. (38.) Hughes, H., Ware, L. L., and Young, F. G.: *Lancet*, 1, 148, 1944. (39.) Jacobs, H. R.: *Proc. Soc. Exp. Biol. and Med.*, 37, 407, 1937. (40.) Janes, R. G., and Friedgood, C. E.: *Endocrinology*, 36, 62, 1945. (41.) Johns, W. S., O'Mulvenny, T. O., Potts, E. B., and Loughton, N. B.: *Am. J. Physiol.*, 80, 100, 1927. (42.) Joslin, E. P.: *New England J. Med.*, 232, 219, 1945. (43.) Kennedy, W. B., and Lukens, F. D. W.: *Proc. Soc. Exp. Biol. and Med.*, 57, 143, 1944. (44.) Kirschbaum, A., Wells, L. J., and Molander, D.: *Proc. Soc. Exp.*

Biol. and Med., 58, 294, 1945. (45.) Koref, O., Vargos, L., Rodriguez, F. H., and Telchi, A.: *Endocrinology*, 35, 391, 1944. (46.) Lackey, R. W., Bunde, C. A., Gill, A. J., and Harris, L. C.: *Proc. Soc. Exp. Biol. and Med.*, 57, 191, 1944. (47.) Leech, R. S., and Bailey, C. C.: *J. Biol. Chem.*, 157, 525, 1945. (48.) Lukens, F. D. W., and Dohan, F. C.: (a) *Science*, 92, 222, 1940; (b) *Am. J. Physiol.*, 133, 368, 1941; (c) *Endocrinology*, 30, 175, 1942. (49.) Lukens, F. D. W., Dohan, F. C., and Wolcott, M. W.: *Endocrinology*, 32, 475, 1943. (50.) Marks, H. P., and Young, F. G.: *Lancet*, 1, 493, 1940. (51.) Minkowski, O.: *Untersuchungen über den diabetes mellitus nach exstirpation des pankreas*, Leipzig, 1893 (cited by Allen<sup>2a</sup>). (52.) Mirsky, I. A.: *Proc. Soc. Exp. Biol. and Med.*, 59, 35, 1945. (53.) Ogilvie, R. F.: *J. Path. and Bact.*, 56, 225, 1944. (54.) Richardson, K. C.: *Proc. Roy. Soc. London, Ser. B*, 128, 153, 1939-40. (55.) Richardson, K. C., and Young, F. G.: (a) *J. Physiol.*, 91, 352, 1937-38; (b) *Lancet*, 1, 1098, 1938. (56.) Ridout, J. H., Ham, A. W., and Wrenshall, G. A.: *Science*, 100, 57, 1944. (57.) Sandmeyer, W.: *Ztschr. f. Biol.*, 31, 12, 1895. (58.) Thorogood, E.: *Federation Proceedings*, 3, 48, 1944. (59.) Van Beek, C.: *Nederl. Tijdschr. v. geneesk.*, 83, 646, 1939. (60.) von Mering, J., and Minkowski, O.: *Arch. exp. Path. u. Pharm.*, 26, 371, 1889. (61.) Warren, S.: *The Pathology of Diabetes Mellitus*, 2nd ed., Phila., Lea & Febiger, 1938. (62.) Weichselbaum, A.: *Sitzungsber. k. Akad. Wissensch., Math.-naturwissensch. Cl.*, 117, 211, 1908. (63.) Weinglass, A. R., Frame, E. G., and Williams, R. H.: *Proc. Soc. Exp. Biol. and Med.*, 58, 216, 1945. (64.) Young, F. G.: (a) *Lancet*, 2, 372, 1937; (b) *Biochem. J.*, 32, 513, 1938.

---

## PREVENTIVE MEDICINE AND EPIDEMIOLOGY

UNDER THE CHARGE OF

JOHN E. GORDON, M.D.

PROFESSOR OF PREVENTIVE MEDICINE AND EPIDEMIOLOGY, HARVARD MEDICAL SCHOOL  
BOSTON, MASS.

---

### AN EPIDEMIOLOGIC APPROACH TO THE STUDY OF THE BIOCHEMICAL MECHANISM OF MOTOR NEURON DISEASE—LANDRY'S PARALYSIS

BY W. LLOYD AYCOCK, M.D., AND GEORGE E. FOLEY  
BOSTON, MASS.

(From the Departments of Preventive Medicine and Epidemiology, Harvard Medical School and School of Public Health)

In both clinical medicine and pathology, emphasis is usually placed on the study of differences in clinical manifestations and in pathologic changes which are exhibited by different diseases. This is well illustrated by the clinical pathologic conference with its stress on differential diagnosis through a searching examination for even minute differences in clinical manifestations or in pathologic lesions. In view of the practical objective of arriving at a correct diagnosis, it is natural that the contrasting of lesions either of a given tissue or cell, or the pattern of lesions in different tissues or cells, in different diseases should occupy first place.

From the point of view of understanding the mechanism through which a given lesion is produced, it may be equally important to contrast or compare different etiologies which produce the same lesion. In other words, the convergent study of a number of diseases or etiologies which produce the same lesion may be as important in one way as the differential study of lesions is in another. In a number of diseases of distinctly different etiologies a highly specific and damaging lesion may occur—motor neuron injury or destruction. Certain of these diseases may not be distinguished so much by any difference in this important clinical or pathologic manifestation but more by the epidemiologic circumstances under

which they occur, by secondary or incidental findings, or by demonstration of the etiologic agent itself.

The motor neuron is one of the most highly individualized cells of the body. Both anatomically and physiologically it is extraordinarily specialized, and the difference in its function from that of cells of the body in general is as great as that between processes as slow as osmosis and as rapid as explosion. It therefore would be expected that this cell is possessed of an equally highly specialized biochemical system.

A number of etiologic agents, the mechanisms of the action of any of which are unknown, all produce changes quite distinct from those which they may produce in other cells. This in itself suggests that these changes may represent disturbances in the biochemical mechanisms which are peculiar to these cells. And since both the disturbances in function and the pathologic changes in the motor neuron caused by any one of a number of etiologic agents takes place under curiously similar circumstances—for example, as a rare complication in a number of virus infections which are otherwise quite dissimilar—the question is raised whether they are the result of a biochemical characteristic which is common to the whole group of agents which may induce selective damage to the motor neuron. The exact mechanism of neuron damage is not known in any one of these diseases. No one of the axone reactions can be removed for exact study from the disease process as a whole of which it is a part. On the other hand, the chemical configuration of the etiologic agent of one, or of a prophylactic or curative agent which counteracts the reaction in another, may be known. In some, there is knowledge of the particular circumstances under which neuron damage takes place or of the factors of susceptibility, inherent or acquired, which influence its occurrence in the course of the different diseases. In others there is a close relationship, either genotypic or phenotypic, between a number of etiologic agents, which although producing otherwise widely different diseases, are all associated with neuron damage. Furthermore, certain of the etiologic agents exhibit a sparring or “absorption” effect toward others. This would suggest that they are capable of occupying and holding identical chemical positions within the cell. And still others may have a common capacity to produce, for example, a given histo-chemical change in the neuron.

Thus, from a conjoint study of a number of diseases which, although differing widely both in etiology and in character, are all associated with the occurrence of a single highly specific cell lesion, and each of which is amenable to study in respect to some one aspect of the production of the lesion in question, it may be possible to “synthesize” a biochemical mechanism which is common to the group.

An understanding of such a biochemical mechanism conceivably might open up new approaches to the control of neuron damage, the one serious effect of a number of diseases, through chemical measures which would be more highly specific in respect to this lesion than either the chemotherapeutic approaches or the individual immuno-biologic procedures, which have heretofore been so largely emphasized but with only partial success.

The review of a number of diseases, in which neuron damage occurs, from the point of view of formulating and exploring this idea is the purpose of this paper. A similar convergent approach was suggested by Shattuck<sup>58</sup> when he stated that alcoholic polyneuritis was “caused chiefly by failure to take or to assimilate food containing sufficient vitamin B,” and “might be properly regarded as beriberi.” Later investigations by Minot, Strauss and Cobb<sup>65</sup> established the validity of Shattuck’s observa-

tions. Some diseases, many cases of which have at times been designated as Landry's paralysis and which might lend themselves to the study of one phase or another of this question are given: poliomyelitis; post-Pasteur paralysis; post-vaccinal encephalitis; post-infectious encephalitis (virus); encephalitis; herpes zoster; post-diphtheritic paralysis; antitoxin and toxoid paralysis (tetanus); tri-ortho-cresyl phosphate; periodic familial paralysis (potassium)—post-nephritic (sodium); tick paralysis; nerve section; nutritional deficiency; so-called infectious neuronitis; myasthenia gravis; progressive muscular atrophy; venom paralysis; lathyrism.

**Landry's Paralysis.** The identity or at least close similarity in the essential lesion in a diverse group of diseases is well illustrated in the story of Landry's paralysis. In a recent textbook<sup>18</sup> it is called "a form of acute, ascending paralysis . . . first described in 1859 and still . . . recognized as a clinical entity." And yet the text goes on to state that the causal agent is not always the same—sometimes the virus of poliomyelitis, epidemic encephalitis or acute infectious neuronitis; botulism or the paralytic form of rabies. That Landry's paralysis is a syndrome of symptoms which occurs in many diseases, rather than a clinical entity, is indicated by the fact that almost every paralytic disease in the diversified group discussed in this paper has been designated as Landry's paralysis when the progress of paralysis has been "ascending" in character. If the celebrated case of ascending paralysis in a person named Socrates had occurred in a later era, and had the tragic epidemiologic and etiologic circumstances not been known, it, too, might well have been called Landry's paralysis. Poison hemlock belongs to the parsley, carrot or celery family. Pharmacologically, the alkaloid concerned is known as coniine, which stands between curare, a depressor of nerve endings, and nicotine, a depressor of nerve ganglia. Coniine poisons both nerve endings and nerve ganglia.<sup>47</sup> As a matter of fact, a recent reëxamination of Landry's original case report ends with the significant query, "Who, in this vitamin conscious age, will deny that Jean Baptiste Grolhier died of *beri-beri*?"<sup>15</sup>

Thus, Landry's paralysis as an entity seems to have been finally differentiated out of existence. This has not been so much by the establishment of differences in the clinical picture or essential lesion, but by the establishment of different etiologies, differences in patterns of distribution or progression of lesions, or by the recognition of one or another incidental symptom or lesion or epidemiologic circumstance. Perhaps, after all, the retention of the term "Landry's paralysis" has become in a sense an expression of something in common in a large group of diseases which even after a long period of differentiation are still not always clearly separable. In 1910, Oppenheim,<sup>77</sup> in the course of a discussion which emphasizes differentiation of the members of a group of diseases in which neuron damage occurs, adds the qualification that ". . . although with Raymond who regards acute anterior poliomyelitis, polyneuritis and Landry's paralysis as a morbid unity and as merely different manifestations of the same disease (*la cellulite-névrite aigue antérieure*) we recognize a genetic relationship." Again, "It would seem then that the genetic relationship between Landry's acute ascending paralysis and this 1930 type of polyneuritis (tri-ortho-cresyl phosphate paralysis) may be very close . . . Further evidence to support this view is that the symptoms and course of Landry's paralysis can be produced experimentally in cats by large doses of tri-ortho-cresyl phosphate."<sup>107</sup>

As late as 1937, when the several diseases under discussion had all been

established as entities on epidemiologic, etiologic as well as clinical grounds, the close similarity in their presenting clinical pictures is well illustrated by the confusion in differential diagnosis which arose in cases occurring in "The Strange Durban Epidemic of 1937," and in those referred to in a report received during the epidemic that a French ship, the "Jean L.D.," which had recently called at Durban, was adrift in the English Channel with all the crew paralyzed. A Harley Street neurologist on a visit to South Africa at the time gave his "considered opinion" that the epidemic was one of atypical acute poliomyelitis. Others thought the disease might be ginger paralysis, but there was, in fact, no connection between the cases and the consumption of Jamaica ginger; many favored a diagnosis of toxic polyneuritis. The occurrence of the disease in the Durban outbreak mainly, but not entirely, in 5 foci gave strong support to the idea of an infectious origin. To deepen the perplexity, 2 cases of polyneuritis of the arsenical type cropped up at one of the foci at the critical period. Other possibilities considered were the Guillan-Barré syndrome and tick paralysis. Thus, the differential diagnosis of the presenting clinical picture remained obscure until an ingenious epidemiologic study revealed that paralysis in all cases had been preceded by 10 to 12 days by nausea and vomiting, and that in turn all cases could be associated, not with the consumption of the same food, but with one or another article of food consumed at one place or another, but all containing one ingredient coming from a single source. Further inquiry revealed that 1 of 15 drums of a particular brand of cooking oil evidently had been contaminated with tri-ortho-cresyl phosphate, by the packing of cooking oil in an uncleaned barrel which had contained lindol.<sup>84</sup>

**The Motor Neuron.** Not so many years ago, anatomy was restricted to the descriptive study of the arrangement of tissues and cells into organs as a basis for an understanding of the function of the organ; and histology to the arrangement within the cells of morphologic constituents largely because of the appearance that they assumed under various staining techniques devised to render one or another of them visible under the microscope. Even here, the nature of these cell constituents was important chiefly in that it provided a reaction—chromophobe or chromophil—which served to differentiate cells primarily in terms of the particular staining technique being used. Similarly, the almost universal use of "chromatolysis" in pathologic descriptions of the diseases discussed in this paper says little beyond the fact that chromatin has lost its affinity for basic dyes.

The motor neuron reaches the highest degree of anatomic and physiologic individuality. It, unlike any other cell of the body, has sacrificed its power of reproduction in its process of specialization. Its long processes, dendrites, and axones are protoplasmic continuations of the cell structure. In the viscid cytoplasm, many fine granules are visible. Some of these are glycogen, others, somewhat larger, are mitochondria. When basic dyes are used, large chromatophilic bodies of variable size and arrangement fill the cytoplasm. These are irregularly shaped bodies with a granular structure. Between them lie only faintly stained spaces through which the neurofibrils pass, but these are visible only after impregnation with silver salts. These chromatophilic, chromidial or tigroid bodies are called Nissl bodies (aggregates of thymonucleic acid), after the great neuropathologist who first described them. They may be arranged in the form of nets, stripes, combinations of nets and stripes, or simply distributed irregularly. Nissl bodies are present in the dendritic processes but not in the axones. Nissl bodies stain with basic dyes like the nucleus and

also contain iron so that they have been considered as extranuclear chromatin. There is probably need for more chromatin in ganglion cells than could be produced in the nucleus, in order to maintain the proper nuclear-cytoplasm relationship. The size of the cells and their long processes makes for an excessively large volume of cytoplasm. Nissl bodies, however, give a positive reaction for thymonucleic acid which is not obtainable from the nucleus. Bodian and Mellors<sup>13b</sup> cite evidence which indicates that Nissl bodies consist of a protein matrix and an attached basophilic component specifically removable by alkalis or ribonuclease, probably a ribonucleic acid. There is no other positive differentiation between nuclear and extranuclear chromatin. Thus, by the application of a number of techniques, the cytoplasm of a motor nerve cell can be shown to be seemingly impossibly filled with either one of several substances. It has been questioned whether the cytoplasmic granules and especially the Nissl bodies are present in the living cell or merely represent the coagulative effects of fixatives on the colloids of the cytoplasm. Only recently have the Nissl bodies and granules been photographed in the living cell under ultra-violet light by Wiemann.<sup>109</sup> Other evidence suggests that they represent living structures even though they exist in a different form in the living cell. During activity, as Dolly<sup>37</sup> has shown, the cells swell and their Nissl bodies fade markedly, suggesting that Nissl bodies represent a vital part of this cell, and are concerned with the special metabolism associated with its extraordinarily rapid changes from rest to complete activity as distinguished from the activity of other cells which may at any given moment be, for example, a kidney tubule cell, comparatively infinitesimal. Cutting the axones of ganglion cells causes chromatolysis. Finally, disease processes produce characteristic and relatively constant changes in these structures. These facts, in addition to their iron content, suggest that Nissl bodies represent a vital part of the cell, and are concerned in the activity of this special type of cell—reservoirs of some substance necessary for its extraordinarily rapid changes.<sup>37</sup> As with the organ, under the older concept, interest centered in the "function," usually the output of a cell, in terms, for example, of secretion or nerve impulse. But anatomy and histology are moving from morphology to the application of methods which are revealing the actual biochemical processes which go on in a cell, an understanding of which will not only explain cell function, but, as well, the biochemical mechanism involved in its pathologic processes. Under this concept, the morphology of the cell relinquishes its dominant position, and becomes the framework upon which the biochemical system of cell physiology, and, in turn, cell pathology operates.

The significance of the morphologic changes involved in chromatolysis—representing profound changes in protoplasmic components and energy relationships of the cell, has acquired new interest with the convergence of various lines of investigation from related fields. The well-known fact that virus activity produces chromatolysis in the affected nerve cell indicates the necessity of knowledge of the localization of materials and chemical reactions within the cell. The relation of cellular physiology to infection is further emphasized by the observation by Howe and Bodian,<sup>45</sup> that cells ordinarily susceptible to poliomyelitis virus are rendered relatively resistant by axone section.

As pointed out by Bodian and Mellors,<sup>13b</sup> the "normal" Nissl pattern is a result of the equilibrium of cytoplasmic nucleoprotein. Depletion of these substances might be interpreted as a degenerative change due to



increased requirements for protein synthesis following cell injury, as, for example, the increased synthesis created by a regenerating axon. To quote Bodian and Mellors:<sup>13b</sup> "The occurrence of chromatolysis in various pathologic conditions in which axon regeneration is not involved, suggests a shift in the balance of a steady state by differential inhibition or acceleration of complex enzyme-regulated reactions. This might be expected to have a variable effect on the many qualitatively different 'neuron species'<sup>34</sup> present in the nervous system, producing the well-known 'differential vulnerability'<sup>96</sup> of different nerve centers to various toxic agents, and in a spectacular fashion to poliomyelitis virus. In addition to the specific production of chromatolytic changes by toxins and neurotropic viruses, interference with enzyme mechanisms by hormonal imbalances<sup>34</sup> or dietary deficiencies might conceivably in extreme cases produce the phenomenon of chromatolysis. Such changes of nerve cells have been reported, for example, in thyrotoxicosis."<sup>23,38</sup>

Some knowledge of the biochemical changes accompanying chromatolysis has been gained from studies on the response of the neuron to axon section. As long ago as 1930, Marinesco<sup>62</sup> reported increased proteolytic activity in chromatolytic cells. More recently Gersh and Bodian<sup>35</sup> reported significant changes in the concentration of cytoplasmic ribonucleotide and protein during chromatolysis, suggesting alterations of enzymatic activity, at least ribonuclease and proteases, and probably other enzymes. Bodian and Mellors<sup>13a</sup> found that phosphatase activity also is affected by chromatolysis, in that an increase above the normal range of activity during the chromatolytic cycle occurs at the time (or a little later) of the appearance of histologic changes. The increased phosphatase activity is confined to the cytoplasm, there being no increase in activity of nuclear phosphatase at any stage of chromatolysis, and is sensitive to pH changes. Activity appears to be increased by nucleic acid, suggesting ribonuclease activity.<sup>13b</sup> Experimentally, it has been observed by Allen and Eiler<sup>3</sup> that crystalline ribonuclease liberates phosphoric acid groups from ribonucleic acid. Bodian and Mellors<sup>13b</sup> suggest a correlation between increased phosphatase activity and increased synthesis of nucleoprotein, since the peak of phosphatase activity in the chromatolytic cycle seems to occur with the height of Nissl body breakdown. A selective action on acid phosphatase activity is exerted by the adenylic acid and nucleotides derived from ribonucleic acid.

Further evidence of the relationship of these complex enzyme reactions to the integrity of the cell can be seen in recent studies on the cytochrome oxidase of normal and regenerating neurons. Potter and Albaum<sup>79</sup> found that cytochrome oxidase was inhibited by ribonuclease. Howe and Mellors<sup>46</sup> reported that the maximum reduction of cytochrome oxidase activity coincides with the maximum refractoriness of the cell to infection with poliomyelitis virus. However, neither phenomenon could be correlated with maximal chromatolysis. Following root section, the cell exhibited no resistance to virus for about 10 days, after which it rises to a high level which lasts for several weeks, or until functional recovery takes place; at which time the cell is no longer resistant. These studies suggest a relationship between cytochrome oxidase activity and resistance to virus infection. As pointed out by Howe and Mellors,<sup>46</sup> there is no reason to believe that chromatolysis is not a manifestation of regenerative processes despite the fact that it occurs in pathologic states in which it obviously represents cell damage. The reversibility of the chromatolytic cycle indicates that the condition is compatible with cell life.

Thus, there is some exact data on the nature and course of chromatolysis and its effect on the physiologic integrity of the motor neuron. On the other hand, knowledge of the nature of the events inducing chromatolysis (other than axone section) is lacking. The term "neurotropic," generally used to explain the peculiar selectivity of certain substances for nervous tissue is almost as vague, insofar as exact knowledge is concerned, as was the term "chromatolysis" prior to the advent of modern histochemical techniques. It seems logical that "neurotropism" probably depends upon the presence in the nerve cell of a chemical substance or function essential to the metabolism of viruses or presenting a specific chemical affinity to the inorganic "neurotropic" substances.

Biochemically, one of the characteristics by which the nerve cell is set apart from other cells, is the synthesis of acetylcholine. Choline acetylase, the enzyme which synthesizes acetylcholine from choline and acetates, is present only in the nervous tissue.<sup>74</sup> This, together with the presence of choline esterase, which decomposes acetylcholine, at or near the surface of a neuron in contrast to the respiratory enzymes which are concentrated in the axoplasm, suggests the concept that acetylcholine metabolism is intrinsically related to the electrical changes occurring during nerve activity.<sup>72</sup>

The metabolism of the phospholipids is intimately related to the formation of acetylcholine. As Nachmansohn and his co-workers<sup>73</sup> recently pointed out, "The changes at the neuronal surface during their activity and their rapid reversal cannot conceivably be effected without energy loss since they must involve processes which are—from the thermodynamic point of view—irreversible, and can only be reversed by the free energy of chemical reactions. If the release of acetylcholine and its subsequent breakdown is responsible for the alterations of the nerve membrane during the transmission of the nerve impulse, chemical reactions must supply the energy for the resynthesis of acetylcholine."

These same authors suggest that the most readily available source of energy for endergonic life processes is the energy-rich phosphate bond. The concentration of phosphocreatine in the nerve cell is as high as that attained in muscle cells. Nachmansohn *et al.*<sup>73</sup> have shown that the breakdown of phosphocreatine preceded by the breakdown of adenosinetriphosphate is adequate to account for the electrical energy released by the action potential of the thermoelectric organ in the electric eel; the energy essential to the original synthesis of phosphocreatine being derived from the oxidation of pyruvic acid or glucose. The adenosinediphosphate formed by the breakdown of adenosinetriphosphate is rephosphorylated by the subsequent breakdown of phosphocreatine. Those authors described this chain of biochemical reactions or the "acetylcholine cycle" as follows: "The breakdown of acetylcholine by choline esterase and eserine is followed by the liberation of a phosphate bond from adenosinetriphosphate. The adenosinediphosphate thus formed is resynthesized to adenosinetriphosphate by the subsequent breakdown of phosphocreatine. The resulting creatine is rephosphorylated either by phosphopyruvic adenosinetriphosphate acting as an intermediate, or by the oxidation of pyruvic acid. The link between the adenosinetriphosphate and acetylcholine may be either acetylphosphate or phosphorylcholine."

These reactions occur under aerobic conditions only in the presence of glucose or pyruvate, while acetylcholine is synthesized from choline and acetate under anaerobic conditions.<sup>74</sup> This latter observation may explain in part the extreme sensitivity of the nerve cell to oxygen. On the other

hand, anaërobic conditions and various respiratory inhibitors appear to inhibit the formation of phospholipid.<sup>101</sup> Any event which disturbs this delicate oxygen balance or inhibits any one of the several enzymes activating the various reactions in the chain, could conceivably disrupt the metabolism of the cell and prevent the formation of acetylcholine. There is some evidence that disturbance between the enzyme and its menstruum can bring about profound changes in the cell. Chromatolysis has been attributed to an enzymatic imbalance resulting in the inability of the cell to replace nucleotide as rapidly as it is expended.<sup>36</sup> Nachmansohn and Machado<sup>73</sup> point out that if pyruvic acid is the precursor of the acetate (acetic acid) utilized in the acetylation of acetylcholine, then inhibition of the formation of pyruvic acid could prevent the production of acetylcholine. That such might be the case is suggested by the inhibition of acetylcholine by sodium iodoacetate which reacts specifically with the sulfhydryl groups contained in the proteins of many enzymes.<sup>72</sup> The activity of phosphatase is inhibited by the action of strong oxidants, perhaps by action on certain amino groups of the enzyme rather than the sulfhydryl group.<sup>90</sup> On the other hand, adenosinetriphosphate is decomposed rapidly by increased phosphatase activity in autolyzed tissue.<sup>51</sup> Adenosinetriphosphate appears to play an equally significant rôle in muscular contraction. As pointed out by Sandow,<sup>85</sup> it is now generally accepted that myosin and adenosinetriphosphate are the most fundamental constituents of muscle tissue. Myosin is the contractile substance and adenosinetriphosphate is the source of chemical energy which activates myosin for mechanical activity. In this cycle, as in that of the nerve cell, the source of energy is the 2 labile phosphate bonds in adenosinetriphosphate. The studies of Englehardt *et al.*<sup>28,29,30</sup> furnish abundant proof that adenosinetriphosphate is the source of energy: (1) myosin acts as adenosinetriphosphatase, specifically catalyzing the hydrolysis of adenosinetriphosphate to adenosinediphosphate and free inorganic phosphate with the accompanying release of chemical energy, and (2) artificially spun fibers of myosin elongate during the hydrolysis of adenosinetriphosphate.

The neurotoxic effect of tri-ortho-cresyl phosphate might be brought about by similar enhancing or inhibiting action on one or more of the enzyme systems involved in the acetylcholine cycle. It is known that tri-ortho-cresyl phosphate exerts an inhibiting action on choline esterase, a property not exhibited by the meta- and para-isomers of this compound.<sup>44a,b</sup> It could be mentioned here that in the opinion of some<sup>2</sup> the viruses behave as biocatalysts, disturbing or changing the course of cellular physiology by catalytic action. Such a view is not as revolutionary as it would have been a few years ago since Stanley<sup>98</sup> succeeded in crystallizing the virus of tobacco mosaic disease. Certainly the similarity of neuron lesions produced by several viruses and certain chemical substances at least suggests a similar mode of action in the nerve cell. As Winslow<sup>110</sup> recently stated, "The discovery by Stanley in 1935 that the virus of tobacco mosaic could be isolated in crystalline form shattered, once and for all, the older theoretical boundaries between chemical and biological 'germs' of disease, and made us realize that the distinction between the 'living' and the 'non-living' world is only a matter of definition—and a definition very difficult to draw. Fracastorius would have accepted this demonstration without surprise; and Liebig would have hailed it with delight."

By no means is it implied that the mechanism is identical in these diseases of varied etiology. As has already been pointed out, the acetyl-

choline cycle obviously presents many points of vulnerability at which it might be attacked by one or another of the groups of etiologic agents, the end-result of any of which could produce an identical or at least closely similar clinical or pathologic result.

**Diseases in Which the Chemical Nature of the Etiologic Agent Is Known.**  
Tri-ortho-cresyl phosphate: "A patient entering a hospital with bilateral motor paralysis of arms and legs gradually grew worse with incontinence and deglutitory paralysis, and died of respiratory paralysis. The most striking factor revealed by histologic examination of autopsy material was the presence of marked degenerative changes in the anterior horn cells and in the peripheral nerve fibers, without inflammatory reaction. Chromatolysis with swelling, eccentric nuclei and occasional shadow cells were also seen in hypoglossal nucleus and in the dorsal motor nucleus and nucleus ambiguus. Nowhere was there any cellular infiltration of endothelial cells, polymorphonuclear leukocytes or phagocytic glia cells; nor was there neuronophagia."<sup>107</sup> So reads the initial case report of a flaccid paralysis which occurred in such great numbers in many parts of the United States in 1930 that it came to be popularly known as "Jake Paralysis," and which after extensive epidemiologic and experimental study was shown to be due to the ingestion of extract of Jamaica ginger which contained tri-ortho-cresyl phosphate.

Withdrawal of the product of the single manufacturer of Jamaica ginger resulted in the prompt disappearance of the disease, except for occasional cases resulting from delayed use of the poisonous lots. The disease again appears under quite different epidemiologic circumstances in 1937 in "The Strange Durban Epidemic," already referred to.<sup>84</sup>

Lillie and Smith<sup>85</sup> showed that triphenylphosphate and tri-ortho-cresyl phosphite produced much degeneration of nerve cells, ranging from tigrolysis to karyolysis, fatty degeneration and vacuolization. With both compounds changes were most marked in the neurons in the anterior horns and Clark's column in the cord, and in the bulbar nuclei. In the main, triphenylphosphate produces in the cat an acute degeneration of the anterior horn cells or when the action is prolonged a moderate to severe fatty degeneration of the myelin sheaths of the peripheral nerves. Indeed, triphenylphosphate poisoning in the cat may be described as a diffuse poliomyelosis, a term used to designate a degenerative process with or without necrosis of nerve cells in brain or cord, but without inflammatory reaction. With the variable degree of involvement of the peripheral nerves it might very well be likened on the basis of its symptomatology and pathology with the clinical condition of acute ascending Landry's paralysis.

In view of the foregoing discussion, it would seem that a knowledge of the manner in which tri-ortho-cresyl phosphate produces neuron damage might even yield information which would suggest specific approaches to the problem of the nature of the as yet chemically undefined agents producing similar—and equally characteristic histologic changes.

Looking for a probable explanation of the mode of action of the neurotoxic phenol esters, the rate of hydrolysis of the phosphates and phosphites of phenol, meta-, para- and ortho-cresyl were compared by Smith *et al.*<sup>93</sup> These compounds have been prepared as mono-, di- and tri-esters, with the esterified bond in the meta-, para- and ortho- positions respectively. All of the compounds, with the exception of the tri-esters of phosphorous and phosphoric acids are readily hydrolyzed into free phenol and inorganic phosphorus, while the tri-esters are stable, being hydrolyzed only by fairly rigorous chemical treatment. These differences in stability are reflected

in differences in toxicity for experimental animals. Smith and Stohlman<sup>94</sup> found that toxicity is proportional to the amount of free phenol liberated upon hydrolysis. The mono-esters are all readily hydrolyzed, the transient symptoms of phenol poisoning in animals appearing coincidentally with the height of free phenol titer in the circulating blood. Similarly, all di-esters elicit phenol poisoning if given in sufficient doses; however they are excreted rapidly and the presence of free phenol in the blood cannot be demonstrated. As would be expected, in view of *in vitro* experiments, the tri-esters are hydrolyzed but little if at all in the body. On the other hand, the tri-esters of meta- and para-cresyl-phosphate (or phosphite) are devoid of toxicity, while the tri-ester of ortho-cresyl phosphate (or phosphite) does not produce the usual symptom of phenol poisoning, but rather exhibits a specific neurotoxic action, producing a flaccid paralysis characterized by lower motor neuron damage in several experimental animals.

In the same report, Smith and Stohlman<sup>94</sup> pointed out that the mono-esters are hydrolyzed in the circulating blood by an enzyme carried by the erythrocyte, while the di-esters are hydrolyzed by enzymatic activity (probably phosphatase in both cases) in the kidney. The free phenol produced by hydrolysis of the mono- and di-esters is conjugated, detoxified and excreted in the urine and stool. On the other hand, the tri-esters are not hydrolyzed, neither are they excreted in any amount in the urine or stool, although the tri-esters could be detected in the circulating blood as soon as 10 minutes after injection. However, they disappeared completely from the circulating blood in about an hour.

Nearly the entire dose of the tri-esters could be accounted for by analysis of tissue collected at autopsy. About 80 % of the dose could be recovered unchanged from the lungs, where it appears to diffuse slowly, and 2 to 3 % could be recovered unchanged from the central nervous system. The distribution of the tri-ortho-ester in the body does not hold with an earlier theory of intraneural hydrolysis.<sup>94</sup> Furthermore, there appeared to be no essential difference in the distribution of the tri-meta-, para- and ortho-esters in the body.

It appears then that the specific neurotoxicity of the tri-ortho-esters is closely related to the presence of an esterified bond in the ortho-position on the molecule. Since the tri-ortho-esters are, for the most part, unchanged in the tissues of the body, it seems that neurotoxicity may be a function of the ester itself. That biologic specificity should be determined by configuration of the molecule is not unusual in itself; for instance, the distribution of sulfanilic acid in the body is largely extracellular; the addition of an amino group (sulfonilamide) or an ethanol group (sulfanilyl-ethanolamide) endows the molecule with a configuration permitting intracellular distribution. Furthermore, if the ethanol group is oxidized to an acid (sulfanilylglycine) the distribution in the body reverts to the original—that of sulfanilic acid.<sup>87</sup> Such interdependencies have been observed in studies of the specific immune response to structurally altered antigens,<sup>53</sup> of bacterial metabolism<sup>111</sup> and more recently in nutritional research.<sup>115</sup>

Para-amino-benzoic acid and sulfanilamide are antagonistic, yet structurally related, differing only in that in the former the carboxyl group replaces the sulfonamide in the latter.<sup>111</sup> These observations led to the hypothesis that the bacteriostatic effect of sulfonilamide might be the result of its substitution for para-amino-benzoic acid at some vital step in cellular metabolism. The dependence of biologic activity on specific chemical structure is further illustrated by the observation that certain

structural changes in para-amino-benzoic acid yields a compound (para-amino-aceto-phenone) which inhibits bacterial growth in competition with para-aminobenzoic acid,<sup>6</sup> itself a growth-promoting substance.

Woolley<sup>115</sup> cited several examples in which structural changes in various vitamins resulted in analogues which inhibited bacterial growth by production of a local "vitamin deficiency," inhibition being preventable or reversible by the addition of sufficient amounts of the metabolite or vitamin concerned. Certain other compounds structurally related to the vitamins may produce the symptoms of a specific deficiency *in vivo*. For example, Woolley and White<sup>113</sup> produced typical thiamine deficiency in mice by the administration of pyriethamine. The deficiency thus produced could be controlled by thiamine in sufficient quantity.

Thus it seems to be possible to produce pharmacologic manifestations similar to the symptoms of specific deficiencies by the administration of analogues of the vitamin involved. As pointed out by Woolley,<sup>115</sup> not all structural alterations produce an inhibitory derivative, as evidenced by the biologic inactivity of most of the compounds structurally related to many of the vitamins. On the other hand, 3 analogues of riboflavin, in each of which the structural change is basically different, all produce riboflavin deficiencies. Little is known of the mode of action of these substances. Whether their activity depends on a blockade of specific receptor substances on or in the cell, thereby preventing the cell from acquiring essential vitamins, or on competition with specific metabolites at a particular enzyme surface is as yet a matter of conjecture. The need for a specific structural "lock and key" correspondence between cell and metabolite analogues is suggested by the affinity of the analogues of para-amino-benzoic acid for the bacterial cell in preference to the cells of the host.<sup>112</sup> As Woolley<sup>115</sup> states, "The fact that several drugs which are active as therapeutic agents against infectious diseases come from this group (analogues of para-amino-benzoic acid) may be related to the relative immunity of animal organisms to such compounds . . . It is not inconceivable, however, that certain specific changes which are brought about by a given vitamin deficiency may be effective and desirable therapeutically." This latter observation is of special interest in view of the increased resistance of animals maintained on vitamin B<sub>1</sub> deficient diets to virus infection.<sup>7</sup> However, it is the exception rather than the rule that the presence of a particular radical in a particular position in the molecule endows a single isomer of a compound with specific neurotoxic activity, while the other isomers are entirely devoid of such toxicity. Three modes of action can be hypothesized (none of which is easily proven) as an explanation for this specificity:

1. Solubility: Differences in intracellular solubility might result in chemical, physical, or mechanical injury to the neuron.

2. Configuration: A marked chemical affinity between tri-ortho-cresyl phosphate (or phosphite) and some substance characteristic of the neuron, resulting in a non-utilizable compound, or loss of a substance essential to the vital economy of the cell.

3. Enzyme poison: Inhibition of an enzyme or enzyme system which is essential to the metabolic or functional activity of the neuron.

**Solubility.** As pointed out by Smith, Engel and Stohlman,<sup>92</sup> among the essential requirements for a neurotoxin are lipid solubility or a course of distribution in the body which brings the substance into intimate contact with the nervous tissues before being detoxified and eliminated. Failure of the body to hydrolyze the meta-, para- and ortho-tri-esters and

the recovery of all 3 isomers from the central nervous system seem to satisfy these requirements. However, the meta- and para-tri-esters are devoid of the neurotoxicity exhibited by the ortho-isomer.

**Configuration.** The delayed action of the tri-ortho-cresyl-esters and its specific neurotoxicity has been attributed to the slow liberation of ortho-cresyl in the nervous tissues,<sup>91</sup> but there is no direct evidence to substantiate this hypothesis. Bauman<sup>9</sup> and Preusse<sup>80</sup> found that ortho-cresyl is in part oxidizable to toluhydroquinone. However, Smith, Engel and Stohlman<sup>92</sup> found that the pharmacologic action of toluhydroquinone did not differ from that of phenol in rabbits and chickens.

The ease with which the ortho-cresyl-esters of an acetate, benzoate and phthalate are hydrolyzed into ortho-cresyl or phenol suggests that the ortho-position alone is not the reason for stability. The substitution of a methoxy group in the ortho-position (guaiacol phosphate) or a hydroxyl group (catechol phosphate) for the methyl group in the ortho-position alters the pharmacologic action of the ester, suggesting that the specific neurotoxic action of the tri-ortho-cresyl-ester is not a property of ortho-cresyl *per se*, but is due to the molecular phosphoric acid-ortho-cresyl aggregate,<sup>92</sup> acting in some manner to interfere with the normal economy of the nerve cells. If these compounds are hydrolyzed or oxidized in the nerve cell, molecular configuration may determine the toxicity of the resulting substance or determine the toxicity resulting from secondary changes.

The experiments of Smith, Engel and Stohlman<sup>92</sup> with intraspinal and intraneural injections of a cresyl compound readily hydrolyzed (catechol phosphate) with the liberation of free phenol, and a phenol derivative (toluhydroquinone) indicates that if phenols or phenol derivatives are brought into intimate contact with nervous tissue without undergoing detoxification, varying degrees of paralysis will result. However, the failure of tri-ortho-cresyl-esters to produce paralysis when injected in the sciatic nerve suggests a more selective affinity and perhaps a different mode of distribution, since activity seems in no way related to phenol content as is the case with the other compounds.

**Enzyme Poison.** As pointed out by Bensley:<sup>10</sup> "Cytoplasm thus has no ultimate structural unit but consists instead of several, perhaps many different types of units, all coöperating in an orderly fashion to produce that ensemble of properties which we call life." Certain of these units, such as the nucleoproteins, lipids, etc., may be essential for the structural integrity of the cell. Others, of highly complex composition, mediate special biochemical processes characteristic of the cell in an extremely complex menstuum. In general, the components of most cells undergo an endless cycle of synthesis and resynthesis—for example, Schoenheimer<sup>86</sup> states, "Nucleic acids . . . are components of large molecules and [are] constantly formed from  $\text{NH}_4$  which has been liberated from amino acids." Enzymatic activity is intimately bound to these reactions. Gersh and Bodian<sup>36</sup> point out that ribonucleic acid in the nerve cell is in a constant state of flux, and that when the enzyme mechanisms involved are disturbed to the degree that replacement of nucleotide is less than rate of expenditure, chromatolysis occurs.

The enzymes or biocatalysts of these reactions often are complex organic molecules possessing a specific structure. Specific function frequently depends on the presence of a single atom—such as the  $\text{Mg}^{++}$  in chlorophyll or the  $\text{Cu}^{++}$  in mushroom polyphenol oxidase. Frequently, the coenzyme is loosely bound to its carrier—many can be modified by

the simple detergents. Modification or inhibition of an enzyme may be the result of a multiplicity of different effects—reduction in the amount of surface exposed to the reactants, chemical affinity, oxidation or reduction, changes in configuration, surface tension, electrical potential, viscosity, or simple pH, etc. Fisher<sup>33</sup> stated the case well when he said, "Enzyme and substrate must be adjusted to each other like lock and key." The direction of cellular physiology thus seems to depend upon the delicate balance between substrate and enzyme—anything that affects this balance might interrupt, inhibit or change the course of continuous cycle of biochemical change essential to the specific function of the cell. Berzelius<sup>11</sup> anticipated this when he wrote, "Several single and compound bodies, soluble and insoluble, have the property of exercising on other bodies an action very different from chemical affinity. By means of this action they produce, in these bodies, decompositions of these elements and different combinations of the same elements to which they themselves are indifferent."

In the complex physiologic and biochemical cycles of the nerve cell, there are several enzymatic systems intimately interrelated—a disturbance in any one of which might disrupt the function of the cell as an organized unit. It is known that tri-ortho-cresyl phosphate exhibits an inhibiting effect on choline esterase—a property which the meta- and para-isomers of this compound do not possess.<sup>44a,b</sup> An interruption of the acetylcholine cycle at this point or by the inhibition of one or more of the various other enzymes at other links in the chain might produce the changes characteristic of nerve cell damage. Indeed, myasthenia gravis may be characterized by a defective synthesis of acetylcholine.<sup>70</sup>

**Lathyrism.** Among the earliest descriptions of paralytic disease is found Hippocrates' observation that prolonged ingestion of a certain kind of "pea" is liable to produce paralysis. "At Ainos, all, men and women, who ate continuously of peas, became impotent in the legs, and that state persisted."<sup>40</sup> The seeds of *Lathyrus sativus* have been used for centuries as food, especially in time of famine, by the people of Italy, France, Algeria and India, often resulting in widespread outbreaks of paralysis. It is said that as early as 1671 the Duke of Würtemberg issued an edict against their use in the manufacture of flour.<sup>99</sup> The medical writings of almost any era contain description of this paralysis.

Following ingestion of steamed or partially cooked seeds, a deep-seated paralysis affecting the extremities develops in a few of those exposed. Prolonged feeding maintains the paralysis, resulting in subsequent development of the characteristic tabetic or ataxic gait.<sup>100</sup> If maintained by continuous feeding, paralysis may ascend, resulting in death from respiratory failure. Histologic studies in man are unsatisfactory, but in the opinion of many observers,<sup>99</sup> the action of the toxic substance is exerted primarily on the motor end-plates and the motor neurons. Paralysis is temporary unless maintained by repeated exposure. Even after paralysis has developed, recovery is prompt if the seed is removed from the diet.

Lathyrism presents another example of a motor neuron disease in which the chemical nature of the etiologic agent is known. Dilling<sup>24</sup> reported that the toxic principle of *Lathyrus sativus* seeds consists of 2 alkaloids, a Group II and a Group IV alkaloid by the Stas-Otto process. The solubility of the toxic principle in boiling water perhaps explains the observation that boiled peas are non-toxic.<sup>99</sup> The Group II alkaloid acts on the voluntary peripheral nerve endings resulting in a loss of excitability, while



the action of the Group IV alkaloid is similar to that of veratrine, affecting the spinal cord primarily, reducing direct muscular excitability. Characteristic paresis can be produced in frogs and mice.

The etiologic agent of Lathyrism appears to be capable of interfering with the physiologic function of the nerve cell in either one or both of two places—either at the motor end-plate or in the neuron itself. The exact manner in which these alkaloids disturb the metabolism of nervous tissue is as yet unknown, but it seems reasonable that paralysis is produced by their action on one or more of the enzyme systems characteristic of the motor neuron.

**Vitamin E Deficiency.** Vitamin E appears to enhance phosphorylation.<sup>67</sup> Torda and Wolff<sup>103</sup> suggested that vitamin E acts on the sulfhydryl groups in choline acetylase, and suggested that this substance or alphanatocopherol may be part of a coenzyme involved in the synthesis of acetylcholine from choline since this latter substance occurs as a constituent of phospholipid. Biochemically, vitamin E behaves as an anti-oxidant, preventing the auto-oxidation of fats.<sup>64</sup> The rôle of vitamin E in the synthesis of acetylcholine probably is related to the paralysis in suckling rats from vitamin E deficient mothers<sup>64</sup> and rats fed a vitamin E deficient diet.<sup>17,83</sup>

Unlike most of the paralyses considered here, vitamin E deficiency paralysis in rats is irreversible, perhaps due to the prolonged exposure to auto-oxidizing fatty acids.<sup>64</sup> However, its prevention by wheat germ oil and vitamin E concentrates has been confirmed repeatedly.<sup>63,68,76</sup> Interestingly enough Singer<sup>89</sup> reported hypoplastic thyroids in vitamin E deficient rats, the thyroid becoming normal with administration of vitamin E. Vitamin E deficiency paralysis in rats might be compared with periodic familial paralysis in that both result from specific deficiencies of known chemical substances, but unlike familial paralysis, which is reversible by the administration of potassium, vitamin E therapy does not alter the course of E deficiency paralysis. There are these 2 instances in which the absence of a chemically defined substance results in paralysis, while in another instance, the presence of a chemically defined substance (tri-ortho-cresyl phosphate) affects the same end-result.

**Diseases in Which the Chemical Nature of the Etiologic Agent Is Unknown.** *Tick Paralysis.* Tick paralysis, first described in 1898<sup>1a</sup>, is a disease usually following the course of Landry's ascending paralysis, and is associated with the bite of any one of a number of species of ticks. The more rapidly the tick feeds, the more rapid is the progression of paralysis. Usually, however, paralysis appears only after the tick has fed for some time, suggesting a phenomenon similar to the reactivation of the rickettsia of Rocky Mountain spotted fever by the spring feeding of *Dermacentor*.<sup>1b</sup> The "toxin" may be injected up to the 6th day of feeding and apparently can be exhausted from the tick since ticks taken from paralyzed patients may fail to produce paralysis in experimental animals.<sup>1b</sup>

Histologically, tick paralysis is characterized by motor neuron damage, with lesions in the anterior horn cells of the spinal column. The "venom" of one species, *Ixodes holocyclus*, appears to be specific for the vagus center and synapses.<sup>1a</sup> The female, not the male tick bite, produces paralysis, the "toxin" perhaps being carried in the ova.<sup>1b</sup> Following parenteral introduction of triturated tick eggs, *Rhipicephalus sanguineus*, *Hyalomma Scupense*, *Boophilus calcaratus*, *Rhipicephalus bursa* and *Dermacentor andersoni*, toxic symptoms develop in guinea pigs, rabbits and mice.

The most striking characteristic of tick paralysis is the dramatic recov-

ery following removal of the tick. If the tick is removed before paralysis develops, symptoms may be mild and transient. The prompt reversal of the paralyzing process by removal of the tick suggests that the toxin might be an alkaloid.<sup>1b</sup> Although the nature of the etiologic agent is as yet unknown, tick paralysis is characterized by 2 phenomena common to other diseases of this group, neuron damage and reversibility.

**Diseases in Which the Chemical Nature of the Therapeutic Agent is Known.** *Periodic Familial Paralysis.* The whole picture of periodic familial paralysis, its epidemiology, pathogenesis, clinical manifestation, therapy and prevention is vividly included in the report of a single case:<sup>48</sup>

"A young infantry officer, wounded late in 1943, was active and ambulatory and expected to be evacuated to North Africa the next day for further treatment; however, in the morning he was unable to lift either leg or move feet or toes. The left forearm was in a cast. The left biceps contracture was stronger than the right. All other deep tendon, periosteal and superficial reflexes were absent. He was amused at the interest shown in his case and indifferent toward the paralysis, remarking, 'Several generations of my family have had this paralysis periodically and all I will need is some potassium chloride.' He took a tablespoonful of the crystals and within an hour the deep tendon reflexes returned, the superficial ones, in an hour and one-half; in two hours he was up and very active. Now he is back in active service.

"This officer over a period of years had many similar attacks of paralysis, some lasting for twenty-nine hours. His case had been diagnosed variously as 'Hysteria,' 'Nothing wrong anywhere,' 'Physically O.K.;' no treatment recommended.' A non-military clinic, however, having made a 'new diagnosis,' the patient started taking potassium chloride.

"In almost four years in the Army, he had been a corporal, sergeant, expert with pistol, M-1, '03, LMG, grenade, bayonet, and in mine and demolition work. He had been wounded once before and has since been wounded a third time, promoted, and awarded the Bronze Star and the Silver Star. He carried a four-pound sack of potassium chloride in his bedding roll and quarter-pound sacks in his combat clothes but, when wounds brought him to the hospital, his potassium had been left behind. He has observed that when on high carbohydrate diet, more potassium chloride is required, more when on B rations than when on C rations, and also more in summer. He carries two canteens of water to wash down the crystals of potassium chloride, taken ordinarily every two to nine days. Sometimes he goes for a month without any, taking it only when he feels himself 'stiffening up.'

"The patient's father died in an attack of family periodic paralysis at the age of 37. He, too, realized the hereditary nature of his ailment. A chart compiled from data 'in the letters' shows that nine members in various generations in this family have been afflicted with this disease."

*Myasthenia Gravis.* As summarized by Viets,<sup>106</sup> in a recent review of myasthenia gravis the formulation of the chemical mediation theory of the transmission of nerve impulses across a synapse by the peripheral release of a specific agent, first suggested by Otto Loewi<sup>58</sup> in 1921 to explain the actions of the autonomic nerves on their effector organs and later expanded by Dale, Feldberg and Vogt<sup>20</sup> to account for a similar reaction at the end-plates of motor nerves to voluntary muscles; the discovery in 1934-1935 by Walker<sup>108</sup> of the therapeutic effects of physostigmine and prostigmine (neostigmine) in alleviating the symptoms of myasthenia gravis, and the stimulation given by Blalock,<sup>12</sup> whose removal of the

thymus in 1941 in cases of myasthenia gravis reopened the whole controversial subject of the relation of the thymus to this disease.

The "vagus substance" first suggested by Loewi was thought to be acetylcholine by Feldberg and Kraye.<sup>31</sup> This was indeed proved to be the case by Dale,<sup>19</sup> and we know that acetylcholine is a necessary constituent at the synapse for the passage of the nervous impulse.<sup>70</sup> Continued development showed that an enzyme also was present, choline esterase, whose specific function it was to split acetylcholine by hydrolysis and thus prevent the continued transmission of a nerve impulse to an individual muscle. Choline esterase, moreover, was found widely disseminated in the blood and body tissue. It is this enzyme that is temporarily inactivated by physostigmine and its closely related drug, neostigmine. The subject of chemical mediation is still a field of intensive investigation.

Three other drugs are commonly used in the treatment of myasthenia gravis: ephedrine sulfate, potassium chloride and guanidine hydrochloride. Ephedrine sulfate, known for many years as a valuable form of treatment, is a useful adjunct to neostigmine. Its effectiveness is about 10 or 15% of that of neostigmine. It is possible to maintain a few patients entirely on this drug if their symptoms are not very severe or if they are in a prolonged partial remission. Potassium chloride has a mild effect on the symptoms of myasthenia gravis in a small percentage of the patients. Guanidine hydrochloride has a considerable effect on the symptoms of myasthenia gravis.<sup>25</sup>

Following the work of Blalock,<sup>12</sup> a number of patients have been subjected to thymectomy in recent years. Thymomas have been found in 4 patients. Hyperplasia of the thymus was found in 3, and the thymus appeared normal, although persistent, in 8 other cases. Of the total group of 15 having thymectomy, some are now in their 2nd and 3rd year following operation. Two are considered as in complete remission, 2 more are distinctly improved, 3 are moderately improved, 1 slightly improved, and 3 have been operated on too recently to be evaluated.

Thus in myasthenia gravis response to maintained drug therapy as well as its thymus relationships, suggests an inherent fault in the metabolic requirements for the "acetylcholine cycle."

**Common Denominator.** When a number of diseases, all distinguishable either etiologically, clinically, pathologically, or epidemiologically, are considered from a convergent rather than a differential point of view they are found to possess one feature in common. The etiologic agents in these diseases are diverse in nature, clinical manifestations are equally diverse and pathologic changes in various organs—tissues are distinguishable in patterns representative of the particular disease. But all are characterized by motor cell damage. The likelihood that the mechanisms involved in the production of this common lesion are related is suggested by other features which numbers of these diseases exhibit. Many of these already have been indicated. Without attempting to assemble all the similarities here, attention may be called to two characteristics which afford some idea of the character of the biochemical mechanism involved.

**Reversibility.** That the reaction responsible for nerve cell dysfunction is reversible is strikingly shown in the prompt and startling recovery of tick paralysis upon removal of the tick; in familial periodic paralysis in its response both therapeutically and prophylactically to the administration of potassium chloride; the effect of potassium chloride and prostigmine in myasthenia gravis and as well in a more or less general tendency

of other types of paralysis—notably virus infection—to improvement or recovery. A more striking example is the tendency of bulbar poliomyelitis with complete paralysis of the deglutitory apparatus to prompt and complete recovery. It is the rule in poliomyelitis for regression from the degree of paralysis at its height to take place.

That neuron damage may be the result of infinitesimal biochemical changes affecting the enzyme systems of the cell, and that normal function may be restored by readjustment of the enzyme menstruum is illustrated by the experiments of Nachmansohn and John.<sup>75</sup> These authors found that certain oxidized amino acids,  $\alpha$ -keto acids, pyruvic,  $\alpha$ -keto glutaric, phenyl and oxyphenyl pyruvic, inhibit the synthesis of acetylcholine by the enzyme choline acetylase. The addition of potassium and glutamic acid to an enzyme system inactivated in such a manner restored 50 to 80 % of the activity, while the further addition of cyanide or the substitution of cysteine for glutamic acid restored activity almost completely. Utter, Werkman and Lipmann<sup>104</sup> have recently shown that the phosphoroclastic split of pyruvic acid into acetyl phosphate and formic acid, as initiated by enzymes derived from *E. coli*, is reversible. Lipmann<sup>57</sup> further reported that the transfer of phosphoryl groups between acetyl phosphate and the adenylic system is an enzymatic reaction, and is reversible.

The effect of potassium on the phosphorylation of the adenylic system appears to be specific. Boger, Lardy and Phillips<sup>14</sup> found that although ammonium can replace potassium *in vitro*, substitution cannot be made *in vivo*. On the other hand, the rôle of sodium in the transfer of phosphorus to the adenylic system may be related to the paralysis seen in acute nephritis.<sup>102</sup>

The effect of potassium on the metabolism of the cell is well illustrated in studies on the susceptibility of tobacco plants to infection with the virus of mosaic disease. Spencer<sup>95</sup> found that while phosphorus was but indirectly related to susceptibility as it influenced growth, potassium exerted a much more direct effect, exerting an effect on susceptibility which was more than that associated with rate of growth. Small doses of potassium increased plant growth and susceptibility, while larger doses stimulated growth to some extent, but markedly decreased susceptibility to the virus.

If one can consider the bacterial cell as a model, as did Lipmann<sup>56</sup> in his analysis of the pyruvic acid oxidation system, interesting analogies—insofar as biologic inactivation and reversibility are concerned, can be drawn. The phenomenon of specific biocatalytic inhibition (perhaps analogous to the effect of tri-ortho-cresyl phosphate on the motor neuron) is becoming the basis of the more modern chemotherapy. The primary requisite of a chemotherapeutic agent is an affinity to the bacterial cell in preference to those of the host. Over and above this selectivity, the acidic and basic property of the bacterial cell makes for additional specificity, *viz.*, the selective action of most of the sulfonamides and penicillin for the gram-positive microorganisms. These chemotherapeutic agents in general exert their effect on a specific metabolic system of the bacterial cell. The principal effect of the sulfonamides, for instance, has been reported to be on some synthetic anabolic process.<sup>105</sup> On the other hand, while observations are far from complete, the effect of penicillin seems not to be an interruption of growth, but an inhibition of cell division.<sup>82</sup> In either case, the reaction is reversible. Even when treated with quantities far in excess of that amount necessary for complete inhibition, these chemotherapeutic agents fail to cause rapid death of the bacterial cell.

The effect of the sulfonamides can be reversed by the addition of para-amino-benzoic acid, that of penicillin by the addition of a substance, probably an enzyme, extracted from a variety of microorganisms, or in either case simply by removing the cell to an environment free of the inhibiting agent.<sup>116</sup>

Dubos,<sup>26</sup> in a recent paper, refers to even more striking examples of reversibility: "One may consider, for example, the case of a suspension of staphylococci or of anthrax spores treated with mercury bichloride; after being exposed for a few hours to the antiseptic these cells fail to grow when transferred to a new medium. If, however, the poisoned culture is treated with hydrogen sulfide, the cells recover their viability even though they have been exposed for seventy-two hours to 1 per cent mercury bichloride<sup>27</sup> . . . A similar phenomenon is observed with a certain basic protein extracted from wheat germ which acts as a powerful antiseptic for yeast and *Lactobacillus casei*. If after twenty-four hours' exposure of these organisms to the toxic protein one adds to the system an adequate amount of a phosphatide, the cells recover their viability and grow; it appears that in this case the wheat protein forms a lipo-protein complex with the phospholipid and is thus dissociated from the inhibited microbial cell<sup>114</sup> . . . One may, on the other hand, effect the equilibrium by adding to the system a substance which possesses great affinity for the anti-microbial agent (*e. g.*, SH-compounds for arsenicals and mercurials, phospholipids for the wheat protein) and thus help in dissociating the antiseptic-bacteria complex. . . . There is, however, a type of inhibition of anti-microbial agents which is still poorly understood and deserves some mention at the present time. It has been observed that several types of phospholipids and a few other surface active substances when added to a suspension of living cells are capable of protecting them against the lethal effect of the subsequent addition of many toxic agents; it has already been seen that phospholipids can form inert complexes with certain toxic agents (wheat protein). It is likely that they can also exert a protective action by becoming adsorbed on the cell surface, perhaps at the very sites at which the toxic agents would otherwise become adsorbed."<sup>8</sup>

It appears that the inactivation of a bacterial cell, with the consequent loss of one or more biologic activities (*e. g.*, synthesis of a vital substance, respiration or reproduction) essential to normal cell function, can be brought about by the specific inhibition of a metabolic system, which frequently can be reversed by the biochemical adjustment of the cellular menstuum. It seems reasonable that the metabolism of a tissue cell can be interrupted and reversed in a similar manner. Indeed, Dubos<sup>26</sup> could have been considering the effect of tri-ortho-cresyl phosphate on the motor neuron when he wrote: "It is obvious that many factors influence the selectivity of an anti-microbial agent: the acidic and basic properties of the cell under consideration, the nature and property of its membrane, its permeability, the relative importance for metabolism and viability of the specific biochemical systems affected by the antiseptic, the activity of the autolytic enzymes, and so on, are all attributes which bear a definite relation to susceptibility."

**Interference.** McKinney<sup>65</sup> found that plants infected with tobacco mosaic virus were resistant to infection with a variant strain of the same virus. Plants often recover from infection to remain carriers of viable virus and are resistant to reinfection with the same or related viruses. Price<sup>81</sup> who reviewed the literature on the acquired immunity of plants to viral diseases states, "Plants recover after an acute attack by produc-

tion of shoots or leaves which appear healthy or show only mild symptoms of disease, which still harbor virus and which are refractory to infection with the virus in question, but not to infection with unrelated viruses . . . With respect to cross immunity, it has been shown with numerous groups of viruses that plant tissues invaded by one strain of a virus are protected from infection with another strain of the virus, but are susceptible to infection with unrelated viruses. The immunity appears to be closely associated with presence of virus in the immune tissues, since there is no evidence that virus free tissues of infected plants are immune. The cross immunity reaction has proved useful for differentiation and classification of plant viruses." Thus it is clear that the resistance exhibited is not a question of cross-immunity, but is related to the presence of the first virus.

Interference between animal viruses was first reported by Magrassi,<sup>61</sup> who observed that rabbits treated with a non-encephalitogenic strain of herpes virus were resistant to subsequent injection of an encephalitogenic strain. Hoskins,<sup>43</sup> the same year, reported similar interference between neurotropic and viscerotropic strains of yellow fever virus in monkeys. Findlay and MacCallum<sup>32</sup> demonstrated similar interference between the viruses of Rift Valley fever and yellow fever in monkeys. Similar interference since has been demonstrated between the viruses of lymphocytic choriomeningitis and poliomyelitis,<sup>21</sup> Virus III and Shope fibroma,<sup>4</sup> different strains of poliomyelitis virus<sup>49</sup> and neurotropic and pneumotropic strains of influenza A virus.<sup>5</sup> These and similar studies have been reviewed in a recent report by Mudd.<sup>69</sup>

That interference is unrelated to the antigen-antibody phenomenon is reemphasized by recent studies by Ziegler and Horsfall<sup>118</sup> on influenza virus in embryonated hen's eggs. These authors reported that there was no evidence of antiviral substances in the embryos in which interference between influenza viruses had been demonstrated. Interference was produced rapidly in the embryo, appearing as soon as 8 to 12 hours after inoculation. These authors concluded that the first virus inoculated interferes with the multiplication of the second, not by multiplication *per se* nor by the action of one virus on the other, but probably resistance to the second virus is the result of a tissue alteration induced by the first virus. The observation<sup>118</sup> that interference can be obtained with a large dose of virus in a shorter time than with smaller doses of the same virus suggests a quantitative relationship. That multiplication is not essential to the interference phenomenon is demonstrated by the studies of Ziegler, Lavin and Horsfall,<sup>119</sup> and Henle<sup>39</sup> who showed that interference with active influenza virus likewise could be obtained with virus inactivated by ultra-violet light. The failure of virus completely inactivated by heat to produce interference<sup>59,118</sup> suggests that a specific molecular configuration, which may be altered by heat, is essential to interference.

Interference between various types of bacteriophages active against the same strain of microorganism has been demonstrated by Delbrück and Luria,<sup>22</sup> Luria and Delbrück,<sup>59</sup> and Luria, Delbrück and Anderson.<sup>60</sup> As Mudd<sup>69</sup> stated, "The lysis of bacteria by bacteriophage may be considered as a virus infection in which the susceptible bacterial cell is the host and the bacterial virus or bacteriophage particle is the parasite. . . . In some instances at least the first step of this critical relationship, the adsorption of virus to host cell may be shown to depend on a specific correspondence in chemical configuration between the virus and components of the host cell surface analogous to that between antibody and cell surface antigen. . . . The first step in the action of bacteriophage

particles on susceptible bacterial cells is specific adsorption of the phage particle to the surface of the bacterial cell. This adsorption must depend on a lock to key correspondence between the pattern of certain molecular configurations on the surface of the bacterial cell and the pattern of configurations on the surface of the phage particle. The adsorption of phage to a specific receptor site on the bacterial cell is analogous to the combination of antibody with antigen at the surface of the bacterial cell. Each depends on a specific surface configurational correspondence. . . . In the work cited a beginning has been made in discovering the all important events that are involved in the parasitization of a host cell by an intracellular parasite. In the case of bacteriophagy at least it seems clear that the initial event is a specific adsorption of the phage particle to bacterial host cell, this combination, like that between antigen and antibody, being determined by specific configurational relationships. This adsorption of phage particle is followed by profound alterations in the metabolic events which occur within the parasitized cell. Some at least of the consequences have been detected: (1) The host cell may become altered in such a way as to make it refractory to super-infection with similar or competing virus particles . . . (2) Multiplication of the bacterial host cell may be arrested. . . . (3) Multiplication of the virus within the host cell may occur without lysis (lysogenic strains). . . . (4) Multiplication of the virus within the host cell followed by lysis may occur. To what extent may the relationship of bacteriophage particles to their bacterial host cells be regarded as affording a clue to the relationship of virus particles to susceptible cells of higher animals and plants? Obviously this question can now be answered in only the most tentative way."

There is some evidence that the relation of the virus particle to the host cell may be analogous to that of the bacteriophage to the bacterial cell. "Lock and key" correspondence or specific molecular configuration is suggested by Hirst's observation,<sup>41</sup> that chicken erythrocytes to which influenza virus has been adsorbed and then eluted are no longer agglutinable by the same or different types of virus. More recently Hirst,<sup>42</sup> in a study of the adsorption of influenza virus on cells of the upper respiratory tract, states, "While the data are meager as yet, it is tempting to formulate a tentative hypothesis as to the possible mechanism of the early stages of influenza virus infection of the respiratory cell. It may not be sufficient merely for an inhaled virus particle to come in contact with any point on a susceptible cell, and it may be necessary for it to become attached to a specific receptor substance to gain entrance. Before the virus can infect, it may also have to alter or destroy this receptor substance by means of an enzyme in order to pave the way for penetration and parasitism of that cell. Once the receptor substance is destroyed the virus becomes more firmly bound, parasitizes the cell, multiplies and again appears free in the lung, making possible spread of infection by contiguity. Since the close correlation has been demonstrated between the neutralizing and agglutination-inhibiting power of various human sera, it may be that neutralization consists mainly of covering over that portion of the virus which ordinarily attaches itself to the receptor substance."

In seeking an explanation for the interference between murine and monkey strains of poliomyelitis virus, Jungeblut and Sanders<sup>49,50</sup> state, "A 'blockade' of susceptible cells by nonparalyzing murine virus might render these cells temporarily impregnable to an attack of paralyzing monkey virus because the orderly function of certain enzyme systems, necessary for successful propagation of monkey virus, has conceivably been disturbed by previous contact with murine virus."

In this connection Kunkel<sup>52</sup> reported an instance in which interference between tobacco mosaic viruses was of curative value early in the infection. As suggested by Ziegler and Horsfall,<sup>118</sup> the reciprocal or reversible quantitative nature of interference between two viruses indicate that the viruses involved may be in competition for a substance which exists in the tissue in fixed amounts. Or perhaps the entry of the virus particle interrupts the physiology of the cell in such a manner as to inhibit the synthesis by the cell of a substance essential to the second virus. As pointed out by Mudd,<sup>69</sup> "Increase in parasitic habit among bacteria is in general correlated with loss of metabolic independence, with dependence on growth accessory substances furnished by the host . . . Although the phenomenon of acquired cellular resistance to superinfection would appear to be a consequence of the fundamental mechanisms of reproduction within their host cells of many animal, plant and bacterial viruses, interference does not occur in all instances of viral infection. Thus numerous cases are on record of the infection of individual cells by more than one virus, evidenced by the demonstration, for instance, of specific intranuclear and cytoplasmic inclusion bodies within the same cell. The changes consequent on the parasitization of a cell, in some but not all instances, therefore render that cell refractory to a second intracellular parasite. Although this acquired cellular resistance is a phenomenon separate from humoral immunity, the two phenomena may supplement each other in the total defense against an intracellular parasitic disease."

For example, the supposed immunity to superinfection in syphilis may be an interference phenomenon since resistance to re-infection seems to depend upon the presence of *Treponema pallida*. Brown and Pearce<sup>16</sup> infected a number of rabbits, then "despirochetized" some of them by treatment with arsphenamine after development of the primary chancre. Five days later all rabbits were successfully re-infected with the same strain of *Treponema pallida*. The treated animals developed chancres, the untreated animals did not.

At this time it might be permissible to hypothesize an explanation for the interference phenomenon in terms of the exact data available. It seems significant that susceptibility to virus infection in such widely divergent types of cell as tobacco leaves,<sup>117</sup> bacteria,<sup>97</sup> and primate nerve cells<sup>46</sup> appears to be dependent on an active cyanide-sensitive (cytochrome-oxidase) respiratory system. It could be theorized then, that virus infection produces the same end-result as does cyanide "poisoning" with similar reduction or inhibition of cytochrome-oxidase activity. Such an infected cell then would be resistant to re-infection with the second virus. Similar metabolic requirements of related viruses and divergent requirements for unrelated strains could be the explanation for the failure of unrelated viruses to interfere. Such an hypothesis is in accord with the views of Ziegler and Horsfall<sup>118</sup> and Levaditi's conception<sup>54</sup> of the "macromolecular nature" of viruses—when a molecule of "nucleo-protein virus" modifies the metabolism of a cell, that cell is incapable of propagating "macromolecular particles" of a different virus.

To say that interference is a simple matter of preoccupation is doubtless an oversimplification of a far more complex biochemical phenomenon. There is an illustration of what is in a sense the reverse of interference in the preparation of one site for a more rapid development of vaccinia by previous inoculation with vaccinia at another site. For example, von Pirquet<sup>78</sup> observed that daily successive vaccinations matured at the same time (between the 10th and 13th day), the incubation period for each vaccination being reduced by as many days as had elapsed from the time



of the first insertion. Vaccinations after the 14th day resulted in an immune reaction.

That the mode of action of the various etiologic agents—virus, metabolic or chemical—of the diseases discussed here is at least similar if not identical, is suggested by the similarity of the resulting lesion. The results of Hirst's studies<sup>41</sup> on the failure of various strains of influenza virus to re-agglutinate eluted erythrocytes suggests a similar cell surface reactivity and tissue susceptibility to different strains of the same virus. As Ziegler, Lavin and Horsfall<sup>119</sup> state, "Moreover, in all known instances of interference both viruses share at least a common tissue tropism, although evidence may be lacking that they actually infect identical cells. Despite these facts, it seems unwise to assume that reciprocal interference necessarily indicates biologic relationship, since it may indicate merely that the viruses concerned are each capable of reacting with a single theoretical receptor substance possessed by cells of the susceptible tissue. . . . Consequently, it appears reasonable to assume that reciprocal interference between the influenza viruses depends upon some portion of the virus particles capable of reacting with susceptible cells, possessed in common by influenza and swine influenza viruses."

**Conclusion.** Present knowledge by no means enables the formulation of the exact cause for the lesion which appears as a manifestation in a number of a group of diseases but it is believed that, if the biologic activity represented by this lesion can be reduced to a single principle, progress will be made.

#### REFERENCES

- (1.) Abbott, K. H.: (a) *Proc. Staff Meet. Mayo Clin.*, 18, 39, 1943; (b) 18, 59, 1943.
- (2.) Alexander, J.: *Colloidal Chemistry*, New York, Reinhold, p. 545, 1944. (3.) Allen, F. W., and Eiler, J. J.: *J. Biol. Chem.*, 137, 757, 1941. (4.) Andrewes, C. H.: *J. Path. and Bact.*, 50, 227, 1940. (5.) Andrewes, F.: *Brit. J. Exp. Path.*, 23, 214, 1942. (6.) Auhagen, E.: *Ztschr. f. physiol. Chem.*, 274, 48, 1942. (7.) Aycock, W. L., and Lutman, G. E.: Review in *AM. J. MED. SCI.*, 208, 389, 1944. (8.) Baker, Z., Harrison, R. W., and Miller, B. F.: *J. Exp. Med.*, 74, 611, 621, 1941. (9.) Bauman, E.: *Ztschr. f. physiol. Chem.*, 3, 250, 1879. (10.) Bensley, R. R.: In *Frontiers in Cytochemistry*, Biol. Symposia, Lancaster, Cattell, vol. 10, 1943. (11.) Berzelius, J.: *Jahresberichte*, 15, 237, 1836. (12.) Blalock, A., Harvey, A. M., Ford, F. R., and Lillenthal, J. L., Jr.: *J. Am. Med. Assn.*, 117, 1529, 1941. (13.) Bodian, D., and Mellors, R. C.: (a) *Proc. Soc. Exp. Biol. and Med.*, 55, 243, 1944; (b) *J. Exp. Med.*, 81, 469, 1945. (14.) Boger, P. D., Lardy, H. A., and Phillips, P. H.: *J. Biol. Chem.*, 149, 529, 1943. (15.) Brown, M. R.: *Arch. Neurol. and Psychiat.*, 40, 800, 1938. (16.) Brown, W. H., and Pearce, L.: *J. Exp. Med.*, 33, 553, 1921. (17.) Burr, G. O., Brown, W. R., and Moseley, R. L.: *Proc. Soc. Exp. Biol. and Med.*, 36, 780, 1937. (18.) Cecil, R. L.: *Textbook of Medicine*, 6th ed., Phila., Saunders, 1944. (19.) Dale, H. H.: *Science*, 90, 393, 1939. (20.) Dale, H. H., Feldberg, W., and Vogt, M.: *J. Physiol.*, 86, 353, 1936. (21.) Dalldorf, G., and Douglas, M.: *Proc. Soc. Exp. Biol. and Med.*, 39, 294, 1938. (22.) Delbrück, M., and Luria, S. E.: *Arch. Biochem.*, 1, 111, 1942. (23.) Diamond, I. B.: *Arch. Path.*, 26, 297, 1938. (24.) Dilling, W. J.: *J. Pharmacol. and Exp. Ther.*, 14, 359, 1920. (25.) Dodd, K., Riven, S. S., and Minot, A. S.: *AM. J. MED. SCI.*, 202, 702, 1941. (26.) Dubos, R. J.: *J. Am. Med. Assn.*, 124, 633, 1944. (27.) Engelhardt, H.: *Disinfection*, 7, 63, 81, 1922. (28.) Englehardt, W. A.: *Yale J. Biol. and Med.*, 15, 21, 1942. (29.) Englehardt, W. A., and Ljubimova, M. N.: *Nature*, 144, 668, 1939. (30.) Englehardt, W. A., Ljubimova, M. N., and Meitini, R. A.: *Compt. rend. Acad. d. se., U.R.S.S.*, 30, 644, 1941 (trans. Chem. Abstr., 37, 391, 1943). (31.) Feldberg, W., and Krayner, O.: *Arch. f. exp. Path. u. Pharm.*, 172, 170, 1933. (32.) Findlay, G. M., and MacCallum, F. O.: *J. Path. and Bact.*, 44, 405, 1937. (33.) Fisher, E., and Thierfelder, A.: *Berichte*, 27, 2031, 1894. (34.) Gerard, R. W.: in *Cold Spring Harbor Symposia on Quantitative Biology*, Cold Spring Harbor, Long Island Biol. Assn., 4, 194, 1936. (35.) Gersh, I., and Bodian, D.: *J. Cell. and Comp. Physiol.*, 21, 253, 1943. (36.) Gersh, I., and Bodian, D.: in *Frontiers in Cytochemistry*, Biol. Symposia, Lancaster, Cattell, vol. 10, 1943. (37.) Grinker, R. R.: *Neurology*, Springfield, Ill., Thomas, 1934. (38.) Hechst, B.: *Beitr. z. path. Anat. u. allg. Path.*, 98, 163, 1936. (39.) Henle, W., and Henle, G.: *AM. J. MED. SCI.*, 207, 705, 1944. (40.) Hippocrates: *On Epidemics*, Book 2, Sect. 4, 3. (41.) Hirst, G. K.: *J. Exp. Med.*, 76, 195, 1942. (42.) Hirst,

- G. K.: *J. Exp. Med.*, 78, 99, 1943. (43.) Hoskins, M.: *Am. J. Trop. Med.*, 15, 675, 1935. (44a.) Hottinger, A., and Bloch, H.: *Helv. chim. Acta*, 26, 142, 1943. (44b.) Bloch, H.: *Helv. chim. Acta*, 26, 733, 1943. (45.) Howe, H. A., and Bodian, D.: *Neural Mechanisms in Poliomyelitis*, New York, Commonwealth Fund, 1942. (46.) Howe, H. A., and Mellors, R. C.: *J. Exp. Med.*, 81, 489, 1945. (47.) Discussion of Tick Paralysis: A Review, II Proc. Staff Meet. Mayo Clinic, 18, 62, 1943. (48.) Johnson, J. W.: *Bull. U. S. Army Med. Dept.*, No. 86, pp. 42, 43, 1945. (49.) Jungeblut, C. W., and Sanders, M.: *J. Exp. Med.*, 72, 407, 1940. (50.) Jungeblut, C. W., and Sanders, M.: *J. Exp. Med.*, 76, 127, 1942. (51.) Kerr, S. E.: *J. Biol. Chem.*, 145, 647, 1942. (52.) Kunkel, L. O.: *in Science in Progress*, New Haven, Yale Univ. Press, 1939. (53.) Landsteiner, K.: *The Specificity of Serological Reactions*, rev. ed., Cambridge, Mass., Harvard Univ. Press, 1944. (54.) Levaditi, C.: *Compt. rend. Soc. de biol.*, 136, 331, 1942. (55.) Lillie, R. D., and Smith, M. I.: *Natl. Inst. Health Bull.*, No. 160, 1932. (56.) Lipmann, F.: *Cold Spring Harbor Symposia on Quantitative Biology*, 7, 248, 1939. (57.) Lipmann, F.: *J. Biol. Chem.*, 155, 55, 1944. (58.) Loewi, O.: *Arch. f. d. ges. Physiol.*, 189, 239, 1921. (59.) Luria, S. E., and Delbrück, M.: *Arch. Biochem.*, 1, 207, 1942. (60.) Luria, S. E., Delbrück, M., and Anderson, T. F.: *J. Bact.*, 46, 57, 1943. (61.) Magrassi, F.: *Ztschr. f. Hyg. u. Infektionskr.*, 117, 501, 573, 1935. (62.) Marinesco, M. G.: *Rev. belg. sc. méd.*, 2, 405, 1930. (63.) Mason, K. E.: *Am. J. Anat.*, 52, 153, 1933. (64.) Mattill, H. A.: *Vitamin E in The Vitamins*, Chicago, Am. Med. Assn., p. 575, 1939. (65.) McKinney, H. H.: *Agric. Res.*, 39, 557, 1939. (66.) Minot, G. R., Strauss, M. B., and Cobb, S.: *New England J. Med.*, 208, 1244, 1933. (67.) Morgulis, S., and Spencer, H. C.: *J. Nutr.*, 12, 173, 1936. (68.) Morelle, J.: *Compt. rend. Soc. de biol.*, 108, 804, 1931. (69.) Mudd, S.: *J. Am. Med. Assn.*, 126, 632, 1944. (70.) Nachmansohn, D.: *Yale J. Biol. and Med.*, 12, 565, 1940. (71.) Nachmansohn, D.: *Exp. Med. and Surg.*, 1, 273, 1943. (72.) Nachmansohn, D., and Steinbach, H. B.: *J. Neurophysiol.*, 5, 109, 1942. (73.) Nachmansohn, D., Cox, R. T., Choates, C. W., and Machado, A. L.: *J. Neurophysiol.*, 6, 383, 1943. (74.) Nachmansohn, D., and Machado, A. L.: *J. Neurophysiol.*, 6, 397, 1943. (75.) Nachmansohn, D., and John, H. M.: *Proc. Soc. Exp. Biol. and Med.*, 57, 361, 1944. (76.) Olcott, H. S., and Mattill, H. A.: *J. Biol. Chem.*, 104, 423, 1934. (77.) Oppenheim, H.: *Textbook of Nervous Diseases*, Bruce translation, 5th ed., London, T. N. Foulis, vol. 1, 1911. (78.) von Pirquet, C.: *Klinische Studien über Vakzination und Vakzinale Allergie*, Leipzig und Wien, F. Deuticke, p. 84, 1907. (79.) Potter, V. R., and Albaum, H. G.: *J. Gen. Physiol.*, 26, 443, 1943. (80.) Preusse, C.: *Ztschr. f. phys. Chem.*, 5, 571, 1881. (81.) Price, W. C.: *Quart. Rev. Biol.*, 15, 338, 1940. (82.) Rake, G., McKee, C. M., and Jones, H.: *Proc. Soc. Exp. Biol. and Med.*, 51, 273, 1942. (83.) Ringsted, A.: *Biochem. J.*, 29, 788, 1935. (84.) Sampson, B. F.: *South African Med. J.*, 16, 3, 1942. (85.) Sandow, A.: *Trans. New York Acad. Sci.*, 7, 139, 1945. (86.) Schoenheimer, R.: *The Dynamic State of Body Constituents*, Cambridge, Harvard Univ. Press, 1942. (87.) Shannon, J. A.: *Ann. New York Acad. Sci.*, vol. 44, 1944. (88.) Shattuck, G. C.: *Am. J. Trop. Med.*, 8, 539, 1928. (89.) Singer, E.: *J. Physiol.*, 87, 287, 1936. (90.) Sizer, I. W.: *J. Biol. Chem.*, 145, 405, 1942. (91.) Smith, M. I., Elvove, E., and Frazier, W. H.: *Pub. Health Rep.*, 45, 2509, 1930. (92.) Smith, M. I., Engel, E. W., and Stohlman, E. F.: *Natl. Inst. Health Bull.*, No. 160, 1932. (93.) Smith, M. I., Lillie, R. D., Elvove, E., and Stohlman, E. F.: *J. Pharm. and Exp. Ther.*, 49, 78, 1933. (94.) Smith, M. I., and Stohlman, E. F.: *J. Pharm. and Exp. Ther.*, 51, 217, 1934. (95.) Spencer, E. L.: *Phytopathology*, 25, 178, 493, 1935. (96.) Spielmeyer, W.: *Histopathologie des Nervensystems*, Berlin, Springer, 1922. (97.) Spizizen, J.: *J. Infect. Dis.*, 73, 222, 1943. (98.) Stanley, W. M.: *Bull. New York Acad. Med.*, 14, 398, 1938. (99.) Stockman, R.: *Edinburgh Med. J.*, 19, 277, 1917. (100.) Stockman, R.: *Edinburgh Med. J.*, 19, 297, 1917. (101.) Taurog, A., Chaikoff, I. L., and Perlman, I.: *J. Biol. Chem.*, 145, 281, 1942. (102.) Thorn, G. W.: Personal communication. (103.) Torda, C., and Wolff, H. G.: *Proc. Soc. Exp. Biol. and Med.*, 58, 163, 1945. (104.) Utter, M. F., Werkman, C. H., and Lipmann, F.: *J. Biol. Chem.*, 154, 723, 1944. (105.) Van Niel, C. B., and Luck, J. M.: *Ann. Rev. Biochem.*, Calif., Stanford Univ., Ann. Rev., Inc., 12, 551, 1943. (106.) Viets, H. R.: *J. Am. Med. Assn.*, 127, 1089, 1945. (107.) Vonderahe, A. R.: *Arch. Neurol. and Psychiat.*, 25, 29, 1931. (108.) Walker, M. B.: *Proc. Roy. Soc. Med.*, 28, 759, 1935. (109.) Wiemann, W.: *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 98, 347, 1925. (110.) Winslow, C. E. A.: *The Conquest of Epidemic Disease*, Princeton Univ. Press, p. 376, 1943. (111.) Woods, D. D.: *Brit. J. Exp. Path.*, 21, 74, 1940. (112.) Woolley, D. D., and White, A. G. C.: *Proc. Soc. Exp. Biol. and Med.*, 52, 106, 1943. (113.) Woolley, D. D., and White, A. G. C.: *J. Biol. Chem.*, 149, 285, 1943. (114.) Woolley, D. W., and Krampitz, L. O.: *J. Biol. Chem.*, 146, 273, 1942. (115.) Woolley, D. W.: *Science*, 100, 579, 1944. (116.) Woodruff, H. B., and Foster, J. W.: *J. Bact.*, 49, 7, 1945. (117.) Woods, M. W., and Du Buy, H. G.: *Phytopathology*, 31, 978, 1941; 32, 288, 1942. (118.) Ziegler, J. E., Jr., and Horsfall, F. L.: *J. Exp. Med.*, 79, 361, 1944. (119.) Ziegler, J. E., Jr., Lavin, G. I., and Horsfall, F. L.: *J. Exp. Med.*, 79, 379, 1944.

# BOOK REVIEWS AND NOTICES

## NEW BOOKS

*Pulmonary Tuberculosis in the Adult. Its Fundamental Aspects.* By MAX PINNER, M.D., Chief, Division of Pulmonary Diseases, Montefiore Hospital for Chronic Diseases, New York; Editor, *American Review of Tuberculosis*; Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, New York. Pp. 579. Springfield, Ill.: Charles C Thomas, 1945. Price, \$7.50.

A *Manual of the Aspergilli.* By CHARLES THOM, Collaborator, Northern Regional Research Laboratory; Formerly Principal Mycologist, Bureau of Plant Industry, U. S. Dept. of Agriculture, Washington, D. C.; and KENNETH B. RAPER, Senior Microbiologist, Fermentation Division, Northern Regional Research Laboratory, Bureau of Agricultural and Industrial Chemistry, U. S. Dept. of Agriculture, Peoria, Ill. Pp. 373; 76 figs. Baltimore: Williams & Wilkins, 1945. Price, \$7.00.

## NEW EDITIONS

*An Introduction to Medical Science.* By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH. (F.R.S. (CAN.)), Professor of Pathology and Bacteriology in the University of Toronto. Third Ed. Pp. 366; 125 ills. Philadelphia: Lea & Febiger, 1945. Price, \$3.50.

For reviews of the earlier editions of this excellent work, by an experienced and authoritative writer, see this JOURNAL (August 1937 and August 1941). In this edition, a new chapter has been added on The Principles of Treatment, as well as having the details of treatment considered in connection with each individual disease. "More attention has been paid to nutritional deficiencies, and the section on vitamins has been brought up to date. Amongst the new material may be mentioned the Rh factor, the relation of the sex hormones to cancer of the prostate, and disseminated sclerosis." One is glad to see that even in a work of this size it was found desirable to include a few pages on the Evolution of Medical Science. E. K.

*Technical Methods for the Technician.* By ANSON L. BROWN, A.B., M.D., Director of Dr. Brown's Clinical Laboratory and School for Technicians. Third Ed. Pp. 706, illustrated. Priv. printed, Columbus, Ohio, 1944. Price, \$10.00.

This edition of a work designed for Technicians, in training or qualified, has been thoroughly revised and a new section added, "Important Laboratory Data."

---

## NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHALL, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles, arranged alphabetically according to the name of the first author and should be complete that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

For the balance of the war, 150 REPRINTS will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

OCTOBER, 1945

ORIGINAL ARTICLES

STUDIES ON STREPTOMYCIN IN MAN

I. ABSORPTION, DISTRIBUTION, EXCRETION AND TOXICITY\*†

By HAROLD A. ZINTEL, M.D.

HARRISON F. FLIPPIN, M.D.

ANNA C. NICHOLS

MARJORIE M. WILEY

AND

J. E. RHOADS, M.D.

PHILADELPHIA, PA.

(From the Hospital of the University of Pennsylvania and the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania)

NUMEROUS clinical studies have shown that penicillin possesses remarkable activity against gram-positive bacteria but has no effect on the gram-negative bacilli as a group. Because penicillin is definitely restricted in the range of its antibacterial activities, considerable interest is being focused on other chemotherapeutic agents. Among those of particular interest is the substance obtained from a certain strain of *Actinomyces griseus* called streptomycin. This substance, first described by Waksman,<sup>1,2</sup> is characterized by limited toxicity to animals<sup>3</sup> and by high activity *in vivo*<sup>4,5,6,7</sup> against various gram-positive and gram-negative bacteria.

As a necessary preliminary to the extensive use of this substance, certain studies were undertaken to determine the behavior of streptomycin in patients and to determine the possibility of toxic or side reactions. Two series of experiments, one dealing with the fate of a single dose and the other with the response to multiple doses, are reported in this paper.

\* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania.

† The Streptomycin was kindly supplied to us by Merck & Co., Rahway, N. J.

**Methods and Materials.** Streptomycin concentration was determined by the plate cup method described by Stebbins and Robinson.<sup>8</sup> The fate of a single dose of streptomycin, administered by various routes was studied in 20 patients who for the most part fell into no specific disease category and varied from healthy to seriously ill individuals. Continuous administration of streptomycin was studied in 18 patients suffering from a variety of diseases, including typhoid fever, Rocky Mountain spotted fever, brucellosis, ulcerative colitis, urinary tract infection and *Salmonella oranienburg* infection. When administered orally, the drug was dissolved in sterile water and mixed with milk. For continuous intravenous administration, streptomycin was given in a continuous drip of 5% glucose solution. When a large amount of streptomycin, such as 600,000 units, was given intravenously in a single dose, it was dissolved in 200 cc. of physiologic saline solution and administered over a period of 15 to 20 minutes. For intramuscular injection the streptomycin was dissolved in 1% procain solution to a concentration of 40,000 or 100,000 units of streptomycin per cc. of solution.

All of the patients receiving streptomycin were followed closely for possible toxic reactions. In a subgroup of 10 patients, more extensive studies were undertaken to determine any possible detrimental effects upon the liver, kidney and the blood.

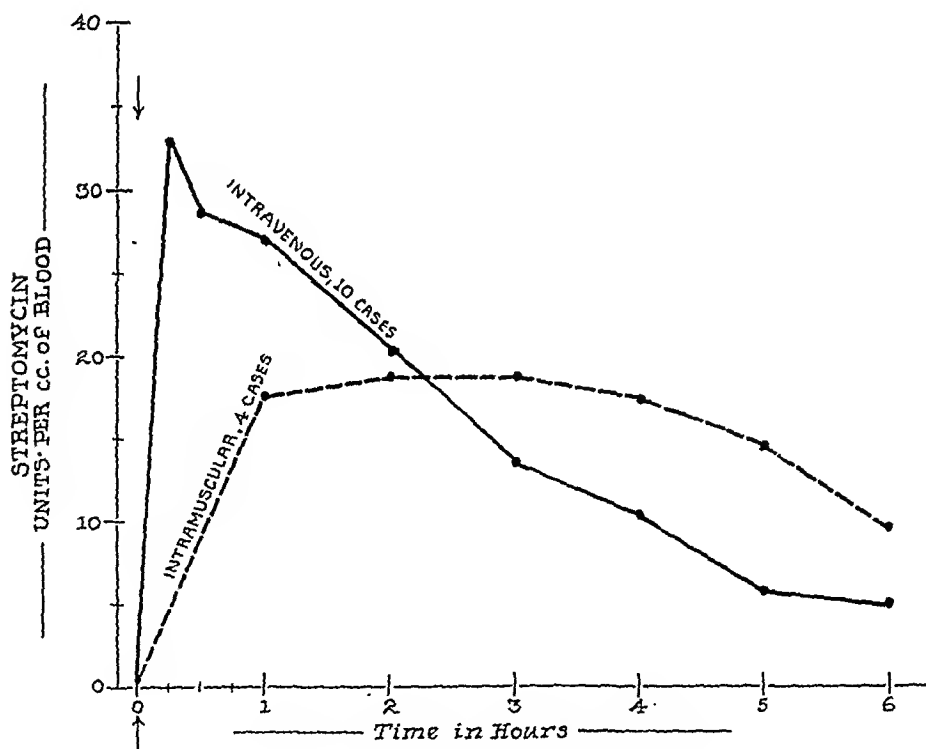


FIG. 1.—Concentration of streptomycin in blood following the parenteral injection of 600,000 units.

**INTERMITTENT PARENTERAL ADMINISTRATION.** Following the intravenous injection of a single dose of 600,000 units of streptomycin, the drug concentration in the blood decreases at a more or less uniform rate for 6 hours (Fig. 1). Fifteen minutes after administration of the streptomycin, the average blood streptomycin level was 32.8 units.

At the end of 6 hours, a small amount of streptomycin, 4.9 units per cc., is still detectable in the blood in the majority of instances.

When the same amount of streptomycin is administered as a single dose subcutaneously in 1% procain solution, the maximum blood level is not attained until between 2 and 3 hours. The maximum streptomycin blood level attained following intramuscular injection was not so high as was obtained following the intravenous injection of 600,000 units. If streptomycin is administered every 3 hours, an additive effect is obtained. In 1 patient who received 375,000 units every 3 hours by intramuscular injection, or a total of 3,000,000 units every 24 hours, the blood streptomycin levels after the 3rd day of administration usually varied between 20 and 60 units per cc. of blood.

**CONTINUOUS INTRAVENOUS INFUSION.** When 3,000,000 units of streptomycin in 3000 cc. of a 5% glucose solution were administered daily by the continuous intravenous infusion method, the blood streptomycin levels usually varied between 20 and 60 units of streptomycin per cc. of blood. The blood streptomycin level during the administration of 1,000,000 units of streptomycin by the continuous intravenous or intramuscular methods varied between 10 and 20 units per cc. of blood. The rate of excretion of streptomycin in the urine was fairly uniform. In the average case two-thirds of the amount administered by continuous intravenous infusion was recovered in the urine. Approximately 2% was recovered in the feces.

**ORAL ADMINISTRATION.** Streptomycin was administered orally at the rate of 1,000,000 units per day to 6 patients. Most of the drug was recovered in the feces. The concentration of streptomycin in the feces increases rapidly during the first few days of treatment. After 4 days of treatment, the stool concentration of streptomycin was usually between 1000 and 5000 units per gram of feces. One specimen from a patient who had received 1,000,000 units daily by mouth for 6 days had a fecal concentration of 9000 units of streptomycin per gram of feces. Only occasionally was any streptomycin found in the blood, and then it was found in minimal amounts, namely 1 to 6 units per cc. of blood. Occasionally measurable levels of streptomycin were found in the urine following the oral administration of 1,000,000 units in 4 cases.

It is obvious that streptomycin passes through the gastro-intestinal wall with difficulty, since when given orally very little appears in the blood, and when administered intravenously only very small amounts of streptomycin are found in the gastro-intestinal tract. It would then seem appropriate to treat those infections in which the pathogenic organisms are found both in the gastro-intestinal tract and in the blood stream by the oral and parenteral routes.

**EXCRETION.** Streptomycin when administered intravenously, subcutaneously or intramuscularly is excreted largely in the urine. Only about 2% of the drug was found in the feces. In 10 cases the urinary excretion of streptomycin was followed for a period of 24 hours after the administration of a single intravenous dose of 600,000 units. From 29 to 89% of streptomycin was excreted in the urine in 24 hours

(Fig. 2). The average 24 hour urine excretion was 66%. Except in those patients who had reduced renal function, the amount of streptomycin excreted varied proportionally to the urine volume.

The highest urine concentration of the samples taken 3 hours after the injection of 600,000 units of streptomycin was 520 units per cc. with an average level for all 10 cases of 353 units per cc. of urine. At the end of 24 hours, the average concentration was 16 units of streptomycin per cc. of urine. It would appear from the curves of the urine concentration and the urinary excretion of streptomycin (Fig. 2) that

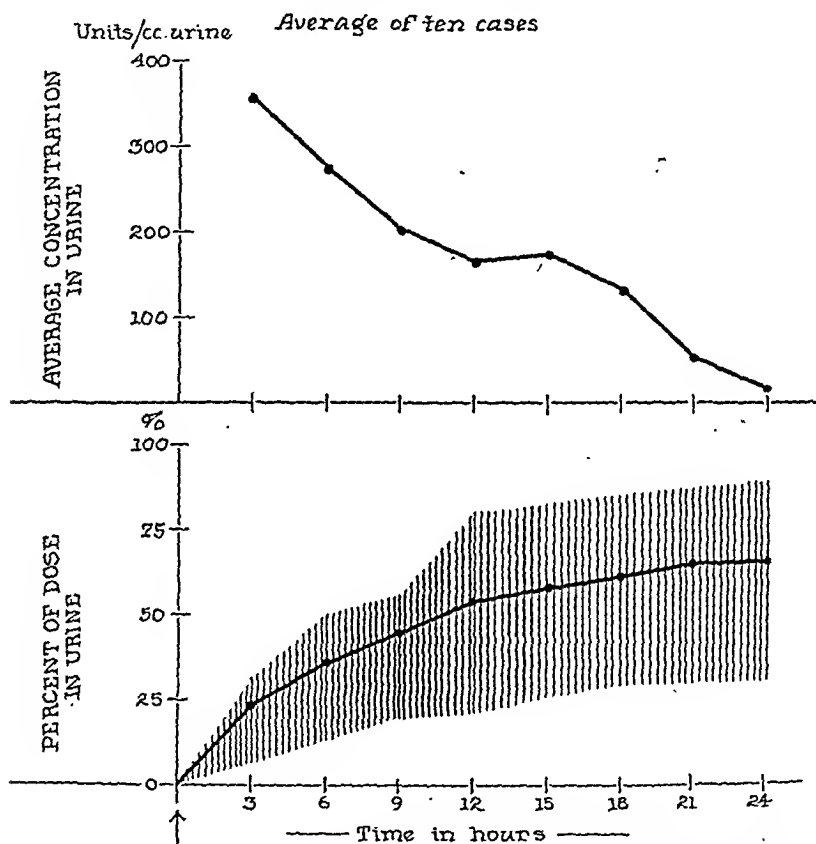


FIG. 2.—Urinary excretion of streptomycin following a single intravenous dose of 600,000 units.

very little more streptomycin would have been recovered if the studies had been carried on more than 24 hours. Therefore, since only 2% of parenterally administered streptomycin is excreted in the feces, and only approximately 66% of the injected amount appears in the urine, it seems logical to presume that some of the streptomycin is retained or destroyed in the body. As stated before, when the drug is administered orally, the chief route of excretion is in the feces.

**DISTRIBUTION OF STREPTOMYCIN IN VARIOUS BODY FLUIDS.** *Peritoneal Fluid.* Streptomycin appears in peritoneal fluid following both intravenous and intramuscular administration. Figure 3 shows the

rate of appearance of streptomycin in peritoneal fluid following the administration of a single intravenous dose of 600,000 units. Streptomycin first appeared in the peritoneal fluid  $\frac{1}{2}$  hour after the drug was administered, and thereafter the concentration of streptomycin increased while the blood streptomycin level was decreasing. This first patient had ascites secondary to cirrhosis of the liver.

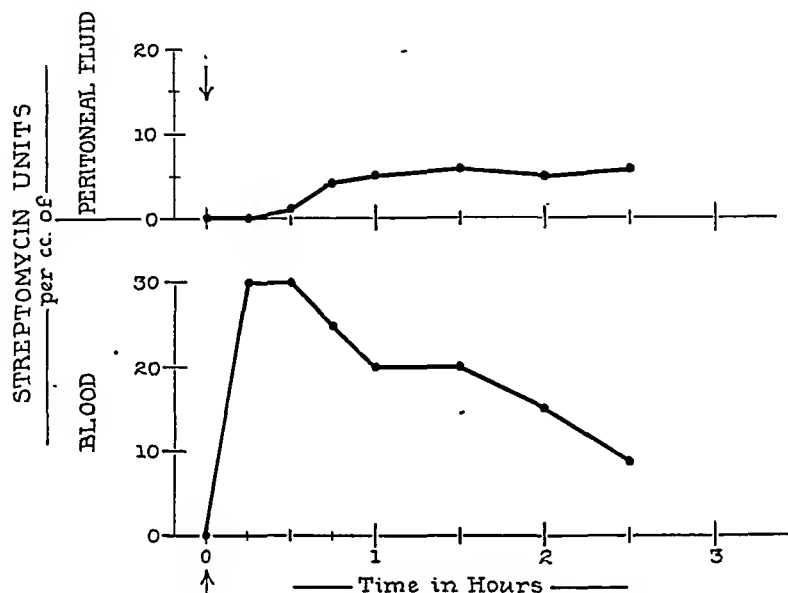


FIG. 3.—Diffusion of streptomycin into peritoneal fluid following a single intravenous injection of 600,000 units.

Streptomycin, 125,000 units intramuscularly every 3rd hour, was administered to a second patient with ascites secondary to carcinomatosis. At the end of 24 hours, the peritoneal fluid level was 23 units per cc., and at the same time the blood level was 15 units per cc. When streptomycin is administered parenterally for longer than a few hours, the blood and peritoneal streptomycin levels are approximately equal. Murphy and Ravdin<sup>9</sup> have shown that streptomycin enters the peritoneal cavity both in the normal animal and in animals with peritonitis. Often the peritoneal fluid streptomycin levels were as high or higher than the blood levels at the corresponding time. The results which they have obtained following the treatment of experimental peritonitis in animals with streptomycin have been good.

*Pleural Fluid.* Three patients with pleural effusions were given streptomycin either by the intramuscular or intravenous routes, and then samples of blood and pleural fluid were obtained simultaneously for determination of their streptomycin content (see Table 1). Streptomycin was found in the pleural fluid of all patients tested. Fifteen minutes following a single intravenous injection of 600,000 units when the blood streptomycin content was 30 units per cc., no streptomycin was found in the pleural fluid. Two hours after the administration of the drug there were 6 units of streptomycin per cc. of pleural fluid. At



the same time a level of 15 units per cc. was found in the blood. When streptomycin was administered over 24 hours, higher pleural fluid concentrations were found. Two patients were given 125,000 units of streptomycin intramuscularly every 3 hours for 24 hours. At the end of the 24 hours, the concentrations found were 18 and 7 units per cc. of pleural fluid. The blood levels in these 2 patients at the time the pleural fluid samples were obtained were 15 and 20 units per cc. respectively.

TABLE 1.—COMPARISON OF BLOOD AND PLEURAL FLUID STREPTOMYCIN LEVELS

Patient	Dose, units	Route	Time interval in minutes from last dose	Blood level, units per cc.	Pleural fluid level, units per cc.
1 . . .	125,000 every 3 hrs. for 8 doses	I.M.	120	15	18
2 . . .	125,000 every 3 hrs. for 8 doses	I.M.	90	20	7
3 . . .	600,000 single injection	I.V.	15	30	0
3 . . .	600,000 single injection	I.V.	120	15	6

*Bile.* Following a single intravenous dose of 600,000 units of streptomycin, maximum bile levels varying between 3 and 7.5 units per cc. have been found, as is shown in Figure 4. At the time these bile specimens were obtained, the streptomycin blood levels were 18 units per cc. in each patient. In 1 patient who received 125,000 units every 3 hours by intramuscular injection for 24 hours, the bile contained 10 units of streptomycin per cc. at the end of the 24 hour period. During the 24 hours, the bile was collected by means of a choledochostomy tube and constant suction. This method has been used in the past for total bile excretion studies. The 24 hour output of streptomycin in the bile in this patient was 3500 units.

TABLE 2.—COMPARISON OF BLOOD AND CEREBROSPINAL FLUID STREPTOMYCIN LEVELS

Patient	Total daily dose in units	Duration of treatment	Route	Blood units, per cc.	Cerebrospinal fluid units, per cc.
1 . . .	600,000 single injection	2 hrs.	I.V.	6.0	.0.0
2 . . .	2,000,000	5 days	I.M.	17.0	1.0
3 . . .	3,000,000	6 days	I.M.	27.0	1.0
4 . . .	1,000,000	24 hrs.	I.M.	13.0	5.0
5 . . .	1,000,000	24 hrs.	I.V.	..	25.0

*Cerebrospinal Fluid.* Streptomycin spinal fluid levels were determined in 5 patients (Table 2). Four of these patients had no evidence of cerebrospinal disease. One of these normal patients (No. 1) was given a single intravenous injection of 600,000 units of streptomycin. Two hours later there was no streptomycin in the cerebrospinal fluid. The 3 remaining patients (Nos. 2, 3 and 4) with apparently normal cerebrospinal systems received from 1,000,000 to 3,000,000 units daily

by intermittent intramuscular injections. The levels obtained in these patients varied between 1 and 5 units per cc. of spinal fluid. One infant (No. 5) with *Hemophilus influenzae* meningitis had a spinal fluid level of 25 units per cc. after having received 1,000,000 units over 24 hours. The blood levels of the patients at the time the spinal fluid specimens were obtained are shown in Table 2.

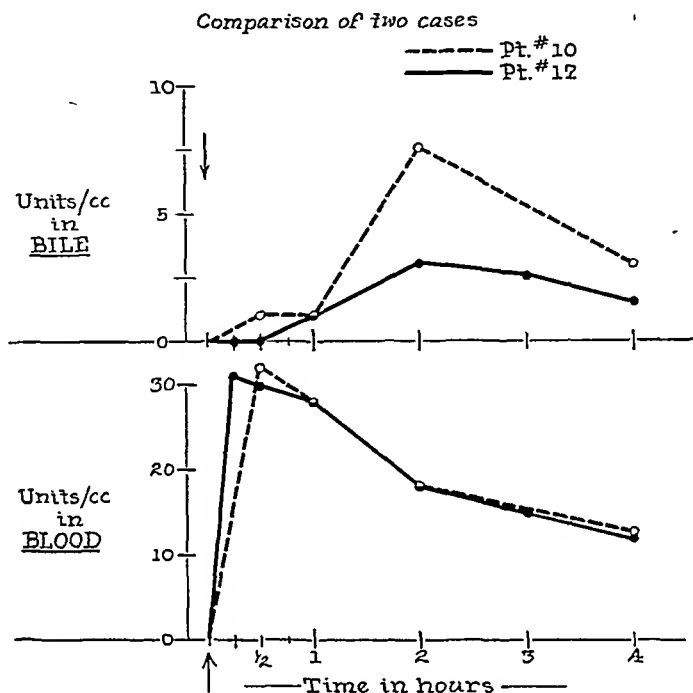


FIG. 4.—Excretion of streptomycin in the bile following a single intravenous injection of 600,000 units.

*Ocular Fluids.* Leopold<sup>10</sup> has demonstrated streptomycin in both the aqueous and vitreous humors of the eye following intravenous, intramuscular and local administration of streptomycin in animals. In 1 patient with glaucoma, 3 units of streptomycin were found per cc. of aqueous humor 30 minutes following the intravenous administration of 600,000 units of streptomycin. A blood specimen taken at the same time contained 40 units of streptomycin per cc. of blood. The secondary aqueous humor removed 3 hours later from the same eye contained 18 units of streptomycin per cc. of aqueous humor.

*Fetal Blood and Amniotic Fluid.* Streptomycin does enter the fetal cord blood and the amniotic fluid. Several patients in labor at term were given 250,000 units of streptomycin either by the intramuscular or intravenous routes. Specimens of fetal cord blood, maternal blood and amniotic fluid were obtained at the time of delivery. In 1 patient the streptomycin concentration was 8 units per cc. of maternal blood, 9 units per cc. of cord blood and 7 units per cc. of amniotic fluid 2 hours after the intravenous injection of 250,000 units. This work will be reported by Woltz and his associates.<sup>11</sup>

**TOXIC EFFECTS. *Immediate Effects.*** The immediate toxic effects have been headache, flushes, transient urticaria and fever. They have been of mild to moderate severity and can be avoided to a large extent by slowing the rate of administration. Local thrombophlebitis may occur after continuous intravenous administration. A single case evidenced flushing of the skin, palpitation and severe throbbing headache when a second course of the drug was started 10 days after the first course was stopped. This same patient had no reactions whatsoever when a more purified form of the drug was used.

***Effect of a Single Massive Dose of Streptomycin on Liver Function.*** In 6 patients an attempt was made to determine whether or not there was any evidence of hepatic damage following the intravenous injection of 600,000 units of streptomycin in a single dose. Estimation of possible liver damage was made by determinations of the prothrombin time; quantitative van den Bergh; total serum cholesterol; serum cholesterol—cholesterol ester ratio; hippuric acid conjugation, bromsulphthalein excretion, cephalin flocculation, thymol turbidity and colloidal gold tests. In all 6 patients these determinations were made 24 hours before a single test dose of 600,000 units of intravenous streptomycin, and the tests were repeated 24 hours after the administration of the streptomycin. Exceptions were in the case of the cephalin flocculation, thymol turbidity and colloidal gold tests which were not repeated until 48 hours after the streptomycin was given. The values obtained are shown in Table 3.

TABLE 3.—EFFECT OF THE INTRAVENOUS INJECTION OF 600,000 UNITS OF STREPTOMYCIN ON LIVER FUNCTION

Patient:	1	2	3	4	5	6	Average
Bromsulphthalein retention, %:							
Before . . . . .	0	0	0	10	0	10	
After . . . . .	0	0	0	5	0	5	
Hippuric acid conjugation, gm. excr.:							
Before . . . . .	1.6	1.7	2.0	2.1	1.5	..	1.77
After . . . . .	1.4	1.2	1.6	1.4	1.6	..	1.29
Van den Bergh, mg. of bilirubin:							
Before . . . . .	0.6	0.3	0.7	0.4	0.5	0.5	0.33
After . . . . .	0.5	0.4	0.4	0.2	0.4	0.2	0.35
Cholesterol, mg. %:							
Before . . . . .	167	171	86	138	123	156	142
After . . . . .	157	155	105	182	147	161	151
Cholesterol in esterified form, %:							
Before . . . . .	58	65	57	59	66	56	60
After . . . . .	58	61	64	73	67	57	63
Cephalin flocculation:							
Before . . . . .	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	
After . . . . .	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	
Colloidal gold:							
Before . . . . .	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	
After . . . . .	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	
Thymol turbidity:							
Before . . . . .	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	
After . . . . .	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	
Prothrombin, % of normal:							
Before . . . . .	80	90	95	70	75	55	77.5
After . . . . .	80	100	75	70	95	70	81.7

Two of the patients studied had liver damage prior to the administration of the test dose of streptomycin as judged by the bromsulphthalein retention test. Neither of these 2 patients showed evidence of further liver damage after the administration of the streptomycin.

In fact both of the patients showed a slight decrease (which was probably insignificant) in the amount of bromsulphthalein which was retained after the test dose of streptomycin. The other liver tests performed were all within normal limits.

*Effect of a Massive Dose of Streptomycin on Renal Function.* Tests of renal function were made on 6 patients before and after the administration of 600,000 units of streptomycin in a single dose intravenously. Blood urea nitrogen, blood non-protein nitrogen and urea clearance tests were performed 24 hours before and were repeated 24 hours after the administration of the streptomycin. The results are shown in Table 4. Changes in the various values obtained were irregularly distributed between increases and decreases so that the averages of the figures obtained in the 6 patients were about the same before and after the administration of streptomycin. In addition, in 12 patients urinalyses were made at 3 hour intervals for a period of 24 hours following the intravenous administration of 600,000 units of streptomycin. There was no evidence of renal damage as judged by the number of red blood cells, white blood cells, epithelial cells or casts in these examinations.

TABLE 4.—EFFECT OF THE INTRAVENOUS INJECTION OF 600,000 UNITS OF STREPTOMYCIN ON RENAL FUNCTION

Patient:	1	2	3	4	5	6	Average
Urea clearance % of average normal:							
Before	..	44	..	107	66	90	76.7
After	..	42.5	..	63	78	93	69.1
Blood urea nitrogen:							
Before	13.3	15	16	7	7	7	10.7
After	10.8	9.5	9.8	9	8	8	9.2
Non-protein nitrogen:							
Before	28	26	23	27	22	20	24.3
After	26	23	25	25	23	25	24.5

*Effect of Streptomycin on Blood.* Platelet, white blood cell and differential white blood cell counts, as well as hemoglobin determinations, were made 24 hours before and 24 hours after the intravenous administration of a single dose of 600,000 units of streptomycin (see

TABLE 5.—EFFECT OF THE INTRAVENOUS ADMINISTRATION OF 600,000 UNITS OF STREPTOMYCIN ON THE BLOOD

Patient:	1	2	3	4	5	6	7	8	9	10	Average
Hemoglobin:											
Before	77	97	89	82	78	80	74	97	89	93	85.6
After	85	96	84	74	75	69	70	95	86	88	82.2
White blood cell count:											
Before	8000	9500	9,300	5000	5500	7000	5400	8700	4000	6000	6840
After	7700	5600	14,200	7400	6600	6000	5800	6400	4000	6200	6990
Neutrophils:											
Before	75	81	68	56	66	68	79	72	78	74	71.7
After	60	70	79	78	66	66	69	81	66	75	71.0
Lymphocytes:											
Before	23	16	19	64	34	32	21	26	18	26	27.9
After	36	28	13	28	28	24	30	19	34	24	26.4
Eosinophils:											
Before	0	1	1	0	2	0	0	0	0	0	0.4
After	0	0	2	0	6	3	0	0	0	1	1.2
Basophils:											
Before	0	0	0	0	0	0	0	0	0	0	0
After	0	0	0	0	0	0	0	0	0	0	0
Monocytes:											
Before	2	2	12	0	0	0	0	0	0	0	1.6
After	4	2	6	4	0	7	1	0	0	0	2.4

Table 5). The changes in the values obtained were variable, however, the average of the values obtained before and after the administration of streptomycin was not significantly different. There was no evidence of toxicity as judged by these examinations of the blood picture.

**Summary.** 1. The blood level of streptomycin following single intravenous injections is better maintained than in the case of penicillin.<sup>12</sup> Detectable amounts were usually present for 6 hours as compared with 2½ to 3 hours in the case of penicillin even when the intramuscular route was used for the latter drug.

2. The principal route of excretion for streptomycin after parenteral injection appears to be the urinary tract.

3. Following parenteral injection, the drug is distributed throughout most body fluids: blood, urine, ascitic fluid, pleural fluid, aqueous humor, vitreous humor, amniotic fluid and bile. Small amounts of the drug appeared in the spinal fluid in healthy individuals, but in a single case of *Hemophilus influenzae* meningitis the spinal fluid contained 25 units per cc.

4. Relatively little transfer of streptomycin occurs between the blood and the lumen of the gastro-intestinal tract in either direction.

5. Following oral administration, levels as high as 9000 units per gm. were found in the feces.

6. Owing to the poor transfer of the drug across the walls of the alimentary tract, it would seem appropriate to use the drug both orally and parenterally in the treatment of infections such as those in which the pathogenic organisms are found both in the gastro-intestinal tract and in the blood stream.

7. Early side reactions have not been alarming, and no late toxic effects have so far been observed. Additional studies are in progress.

#### REFERENCES

1. WAKSMAN, S. A.: Production and Activity of Streptomycin, *J. Bact.*, **46**, 299, 1943.
2. WAKSMAN, S. A., BUGIE, E., and SCHATZ, A.: Isolation of Antibiotic Substances From Soil Micro-organisms, With Special Reference to Streptothrycin and Streptomycin, *Proc. Staff Meet. Mayo Clin.*, **19**, 537, 1944.
3. ROBINSON, H. J., GRAESSLE, O. E., and SMITH, D. G.: Studies on the Toxicity and Activity of Streptomycin, *Science*, **99**, 540, 1944.
4. JONES, D., METZGER, H. J., SCHATZ, A., and WAKSMAN, S. A.: Control of Gram-negative Bacteria in Experimental Animals by Streptomycin, *Science*, **100**, 103, 1944.
5. FELDMAN, W. H., and HINSHAW, H. C.: Effects of Streptomycin on Experimental Tuberculosis in Guinea Pigs, *Proc. Staff Meet. Mayo Clin.*, **19**, 593, 1944.
6. HEILMAN, F. R.: Streptomycin in the Treatment of Experimental Tularemia, *Proc. Staff Meet. Mayo Clin.*, **19**, 553, 1944.
7. HEILMAN, F. R.: Streptomycin in the Treatment of Experimental Infections With Micro-organisms of the Friedländer Group (*Klebsiella*), *Proc. Staff Meet. Mayo Clin.*, **20**, 33, 1945.
8. STEBBINS, R. B., and ROBINSON, H. J.: A Method for the Determination of Streptomycin in Body Fluids, *Proc. Soc. Exper. Biol. and Med.*, **59**, 255, 1945.
9. MURPHY, J. J., and RAVDIN, R. G.: (To be published.)
10. LEOPOLD, I.: (To be published.)
11. WOLTZ, J.: (To be published.)
12. RANDELMAMP, C. H., and KEEFER, C. S.: Concentration of Penicillin in Blood Serum Following Parenteral Injection, *J. Clin. Med.*, **22**, 425, 1943.

## CASE OF STREPTOCOCCUS VIRIDANS PNEUMONIA SUCCESSFULLY TREATED WITH PENICILLIN

BY MAJOR SAUL SOLOMON, M.C., A.U.S.

HQS. ETO, CARE OF OFFICE OF CHIEF SURGEON, A.P.O. 887, NEW YORK

THE introduction of new remedies is ordinarily followed by numerous articles dealing with their clinical application, and until sufficient data have been collected, critical reports of individual cases are of value. This is particularly true when the subject is a rare disease with a high mortality rate, since it is unlikely that any one investigator would have the opportunity to treat a large number of cases. The present report concerns a patient who suffered from pneumonia due to *Streptococcus viridans* (*S. alpha*). He was critically ill and had consolidation of both lower lobes. After an unsuccessful trial of therapy with sulfadiazine, penicillin was employed, and the patient made a complete recovery.

Pneumonia due to *S. viridans* is an uncommon disease, and one which is even less commonly diagnosed. It is most often confused with primary atypical (viroid) pneumonia of undetermined or of virus origin. It is characterized usually by a prolonged severe course with a high mortality rate. Four of the 5 cases reported in a previous article<sup>1</sup> died. The lesion is usually lobar with a tendency to spread to involve more than 1 lobe. A prominent symptom is severe pleural pain. The sputum is thick and mucoid or mucopurulent. The "prune-juice" sputum seen in pneumococcic pneumonia is never observed, and bloody sputum is rare. Leukocytosis may or may not be present. Bacteremia is quite common but does not affect the prognosis. The usual rapid method of sputum typing by the capsule-swelling phenomenon will fail to disclose the *S. viridans*. Sputum culture on blood agar plates is essential for its isolation. Mouse inoculation followed by plating of the peritoneal exudate of the mouse is also a satisfactory method. The bile solubility test should be performed to differentiate pneumococcic from streptococcic colonies, since only the former are bile-soluble. In the cases previously described,<sup>1</sup> the *S. viridans* was cultured from the blood or the chest fluid as well as the sputum. In the present instance the blood was sterile, and no pleural exudate was noted. However, the clinical picture taken in conjunction with the finding of *S. viridans* in the sputum in pure culture on several occasions, was sufficiently convincing to warrant the diagnosis of *S. viridans* pneumonia.

The failure to respond to sulfonamides corresponds with our previous experience with this disease. It is interesting to note that the response of the fever to penicillin was not immediate, though the general condition improved in 24 hours. The temperature fell by lysis 4 days after this treatment was started. This gradual response to treatment has been reported in pneumonia and other conditions treated with penicillin. The positive results in this case agree with the *in vitro* activity of penicillin against the *S. viridans* reported by Dawson and Hobby.<sup>2</sup>

Spread of the pneumonia to involve a fresh lobe during the course of therapy was noted in this case, though it seems likely that this new process was already under way when treatment with penicillin was initiated. The only untoward reactions were a chill soon after the administration of the initial (intravenous) dose of penicillin, and an urticarial rash which appeared after 7 days of treatment.

The following is the abstract of the case giving the details of the clinical course and the therapy:

**Case Abstract.** A 31 year old medical officer was admitted to a general hospital on Oct. 9, 1943. His illness began on Oct. 5 with fever, cough and general malaise. He continued at work until Oct. 8 when he noticed occasional chills, and his temperature rose to 102.4° F.

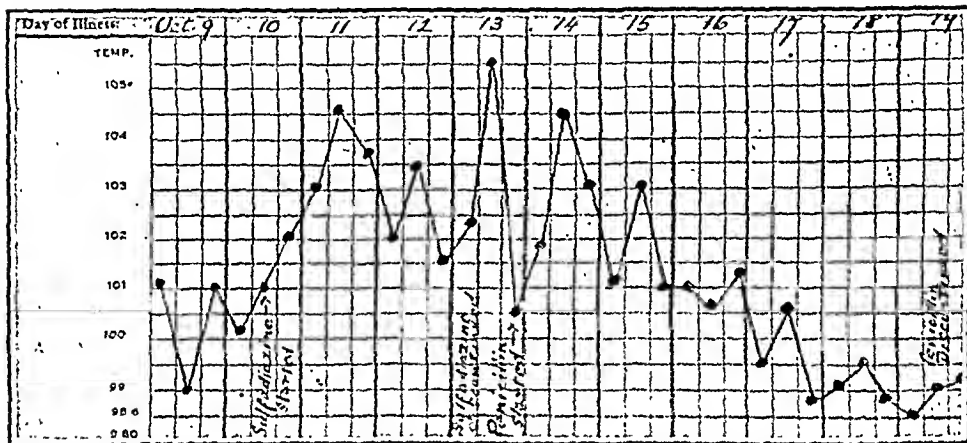


FIG. 1.—Patient's temperature chart for Oct. 9 to 19.

On admission the temperature was 101° F. (see Fig. 1), and the pharynx was mildly injected. The lungs were normal. The rest of the examination was negative. The admission diagnosis was upper respiratory infection. The white blood cells numbered 5500 (57% neutrophils, 36% lymphocytes, 4% monocytes, 2% eosinophils and 1% basophils). The sputum was gray-brown, mucopurulent, and showed numerous pus cells and gram-positive cocci in chains. No pneumococci were found. Culture on blood-agar plates showed *Streptococcus viridans* in pure culture. The organisms were not bile-soluble. A mouse was inoculated with the sputum and survived. Roentgen ray of the chest taken on Oct. 9 was negative. On Oct. 10 the patient had pleuritic pain in the right chest and there was diminished resonance and diminished breath sounds at the right base. Roentgen ray (Fig. 2) showed a patchy infiltration at the right base. Sulfadiazine therapy was started on Oct. 10, the patient receiving 2 gm. orally at 1 p.m. and 1 gm. every 4 hours thereafter. Despite the fact that adequate blood levels were obtained (8 to 9 mg. per 100 cc.), the patient did not respond well. The temperature remained between 103° and 104° F. He was dyspneic and complained of severe pleuritic pain on the right side. He was placed in an oxygen tent on Oct. 11. By this time the classic signs of consolidation in the right lower lobe were present, namely dullness, bronchial breathing and a few rales. The sputum was thick, green and mucopurulent. Culture on blood agar again revealed *S. viridans*. Several samples of the sputum showed no tubercle bacilli. Blood cultures were sterile. The white count on Oct. 13 was 5800 (72% neutrophils, 27% lymphocytes, 1% eosinophils). Another mouse was inoculated intraperitone-

ally with the sputum, and examination of the peritoneal exudate showed *S. viridans* in pure culture. The organisms, as before, were not bile-soluble. Sputum culture on Oct. 15 showed *S. viridans* as the predominant organism with a few colonies of *Staph. albus*. A Roentgen ray taken on Oct. 13 (Fig. 3) showed increased consolidation at the right base. There were physical and roentgenologic signs of congestion at the left base as well.

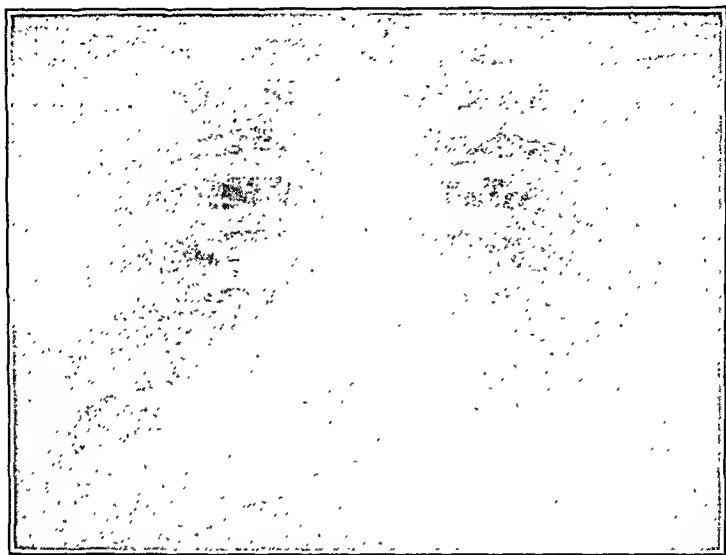


FIG. 2.—Roentgenogram Oct. 10 showing patchy infiltration of right base.

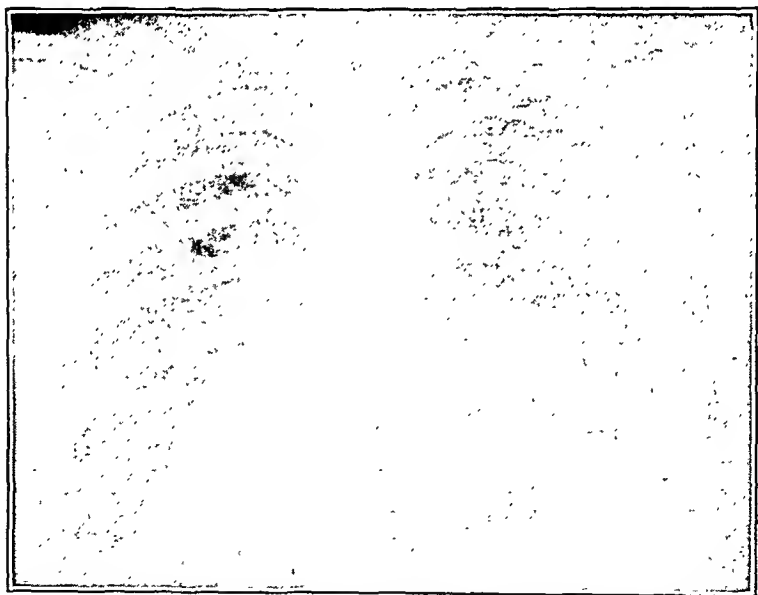


FIG. 3.—Roentgenogram Oct. 13 showing increase in consolidation of right lower lobe and early involvement of left lower lobe.

In view of the fact that the patient did not show any improvement after 72 hours of chemotherapy, sulfadiazine was discontinued and penicillin therapy



was begun. On Oct. 13 he was given 25,000 units of the drug intravenously and 25,000 units intramuscularly. There was no immediate reaction but about 30 min. later he had a severe chill and sinus tachycardia which subsided

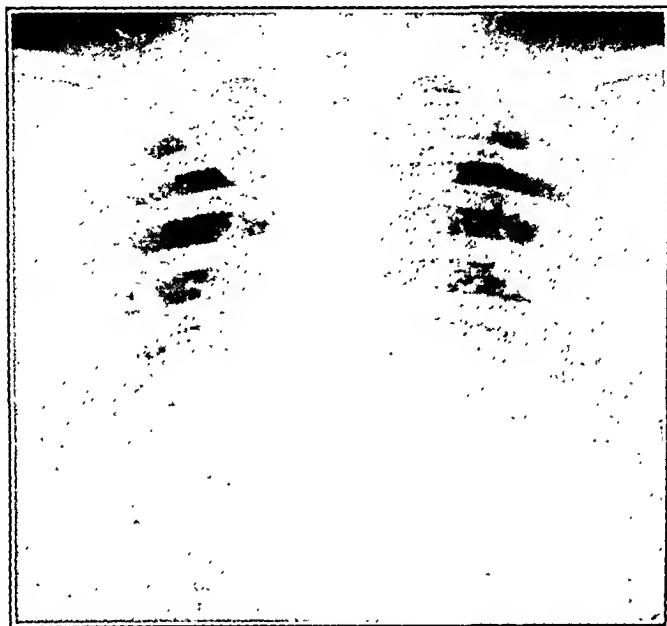


FIG. 4.—Roentgenogram of Oct. 16 demonstrating consolidation of both lower lobes.



FIG. 5.—Roentgen ray Nov. 6. The pneumonia has resolved completely.

following the use of adrenalin and external heat. Thereafter the dosage of penicillin was 15,000 units dissolved in 3 cc. of distilled water given intramuscularly every 3 hours, 8 times a day. This was continued until Oct. 18.

The patient received a total of 690,000 units intramuscularly and 25,000 units intravenously. The response was gradual, the temperature coming down by lysis by Oct. 18 (see Fig. 1). There were no untoward reactions to the penicillin except that on Oct. 19 it was noted that he had an itchy urticarial rash on the face and neck which disappeared in 24 hours. Although the temperature was only slightly elevated, the patient nevertheless felt exhausted, had severe chest pain and cough. It was noted on Oct. 16 that there were signs of consolidation in the left lower lobe. This was confirmed by Roentgen ray (Fig. 4). A blood count on Oct. 19 showed 12,000 white blood cells (73% neutrophils, 24% lymphocytes, 3% monocytes). On Oct. 20 culture of the sputum still showed *S. viridans* as the predominant organism, with a few colonies of *Staph. albus*. The patient made a slow but uneventful convalescence. Roentgen ray on Nov. 6 (Fig. 5) showed complete clearing of the lesion. After a fortnight's sick leave he returned to full duty.

**Summary.** This report concerns a case of *S. viridans* pneumonia, an uncommon disease with a high mortality rate, which does not respond to sulfonamides. The patient was treated unsuccessfully with sulfadiazine for 72 hours, following which penicillin was employed. He responded well and made a complete recovery. It is essential for the diagnosis of cases of this sort to culture the sputum of atypical pneumonias on blood agar plates. Once the diagnosis has been made, it is my experience that sulfonamides are not effective. Penicillin appears to be deserving of further trial.

#### REFERENCES

1. SOLOMON, S., and KALKSTEIN, M.: Pneumonia Due to the *Streptococcus viridans*, *AM. J. MED. SCI.*, 205, 765, 1943.
2. DAWSON, M. H., HOBBY, G. L., MEYER, K., and CHAFFEE, E.: Penicillin as a Chemotherapeutic Agent, *Ann. Int. Med.*, 19, 707, 1943.

---

### OBSERVATIONS ON THE CONTINUOUS INTRAMUSCULAR METHOD OF ADMINISTERING PENICILLIN\*

. BY HAROLD L. HIRSH, M.D.

AND

HARRY F. DOWLING, M.D.

WASHINGTON, D. C.

(From the George Washington Medical Division, Gallinger Municipal Hospital, and the Department of Medicine, George Washington University)

PENICILLIN is now recognized as being highly efficacious in a variety of infections. The problem of how best to administer it, however, remains unsettled. When it is given orally or by rectal instillation, only very minimal amounts enter the blood stream. Repeated intravenous, intramuscular, or subcutaneous injections have been used. When penicillin is injected into the vein, a high blood concentration is immediately attained but, due to the rapid elimination of penicillin by the kidneys, the level in the blood drops rapidly, usually being below detectable levels in less than 2 hours, as shown by Rammelkamp and Keefer.<sup>10</sup> The same authors found that after subcutaneous

\* We wish to thank Miss C. Barbara O'Neil and Miss Ruth L. Mayer for technical assistance.

injection absorption was slow and irregular. Fleming,<sup>3</sup> and also Cooke and Goldring,<sup>1</sup> have recently stated that absorption from a subcutaneous site compares favorably with that following intramuscular injections. This method has not yet had wide trial. Furthermore, concentrated solutions of penicillin may be irritating when given subcutaneously. The method of intermittent injections at intervals of 2, 3, or 4 hours is the most widely used method at the present time, because by this route penicillin can be given simply and fairly adequate blood concentrations can be attained.

When high blood concentrations are required intravenous instillation by means of a "continuous drip" apparatus has been used very successfully. Herrell<sup>5</sup> stated that one-half the amount of penicillin is required to maintain the same serum level by this method as by repeated intramuscular injections. This method, however, requires that the patient possess suitable veins, necessitates immobilization of the patient and frequently results in phlebothrombosis. Rantz and Kirby<sup>11</sup> on administering penicillin subcutaneously obtained plasma levels about 50% as high as by intravenous administration. Others<sup>5</sup> have found this method of administration irregular, variable and uncertain. For these reasons, when the method of constant intramuscular administration was advocated by Harris,<sup>4</sup> by Morgan and his associates<sup>7</sup> and others<sup>6</sup> we began to use it immediately, and up to the present time have employed it in 110 patients. Because this method has worked so well in our hands we are reporting the concentrations of penicillin attained in the blood of the patients we have studied in comparison with those achieved by other methods.

**Material and Methods.** The patients studied were under treatment for a variety of infections. Although some of the blood specimens were obtained during febrile periods and others when there was no fever, we have found no correlation between the patient's temperature and the absorption of penicillin, and have accordingly made no differentiation in this regard. Our procedure has been to calculate the amount of sodium penicillin required for each 12-hour period and to dissolve this in 500 or 1000 cc. of isotonic salt solution. This was placed in the flask connected with a Murphy drip apparatus to which a 2-inch, 18 or 20 gauge needle was attached. The needle was inserted into the lateral aspect of the thigh or into the gluteal muscles and the solution allowed to flow in at a constant rate over the course of 12 hours. When 1000 cc. of solution were used for a 12-hour period, the proper rate of flow was usually 30 or 40 drops per minute. At the end of the 12-hour period the flask was refilled with freshly made penicillin solution. If a point was reached where the fluid was not being absorbed from the muscles, the needle was changed to the other extremity or from the thigh to the buttocks or *vice versa*. Usually the whole setup was changed at the time the needle was reinserted. Such changes were never required more often than every 24 hours, and frequently were not necessary for intervals of 48 or 96 hours. Twenty-five cubic centimeters of 1% procaine were added to each liter of solution when necessary to relieve pain and discomfort. Constant intravenous administration, when used, was also given by use of the Murphy drip apparatus.

Penicillin administered by intermittent intramuscular injection was dissolved so that each cc. of saline contained 10,000 units of penicillin. The injections were made into the deltoid, thigh or gluteal muscles using a 2½-inch, 18 or 20 gauge needle. There was no apparent difference in blood levels regardless of the site of injection. The length of the needle was important, no

penicillin being detectable in the blood stream in the case of one patient when a 1-inch, 26 gauge needle was used for the injection.

Blood serum was obtained from the patients treated by the continuous method at intervals during the period of administration, and for 2 hours after treatment was stopped. From the patients receiving multiple individual injections, blood specimens for penicillin determination were obtained at hourly intervals following three consecutive injections and also at other scattered intervals. Penicillin determinations were done by the method of Rammelkamp.<sup>9</sup>

**Results.** Table 1 shows the blood concentrations attained in patients treated by means of the "intramuscular drip" method, when 100,000 units were given during a 12-hour period. The levels remained fairly constant after the first hour, varying in most instances from 0.078 to 0.312 Oxford units per cc. Occasionally the concentration went as high as 2.5 and as low as 0.0195 units per cc. It will be noted that the method was varied in several different ways. In some patients the injections were given in the thigh muscles, and in others in the glutei. The 24-hour dose of penicillin was dissolved in 1000 cc. of isotonic salt solution in some instances, and in 2000 cc. in others. In some cases, neosynephrin was administered along with the penicillin. No appreciable differences were observed in the blood penicillin concentrations as a result of any of these procedures. The addition of 25 cc. of 1% procaine to each liter of solution to relieve pain and discomfort likewise caused no alteration in blood levels.

Table 2 shows the frequency with which various blood concentrations were achieved by the continuous intramuscular injection of 200,000 units over a 24-hour period as compared with those attained at varying intervals after single intramuscular injections. It is obvious that administration of penicillin by a series of single injections will not maintain levels as high as when the drug is given by continuous injection. When injections of 25,000 units every 3 hours or 20,000 units every 2 hours were given, (200,000 to 240,000 units for a 24-hour period), the median blood penicillin concentration 1 hour after each injection, was not as high as was the continuous level when only 200,000 units were given over a 24-hour period by the continuous method. The blood penicillin levels 2 and 3 hours after a single injection were considerably lower, and often the amount of penicillin present was undetectable by the method used. A concentration of 0.039 units of penicillin per cc. has proved efficacious against most infections susceptible to penicillin.<sup>10</sup> Using this level as a criterion, we found that in 3 patients who were given 25,000 units of penicillin by intramuscular injection every 3 hours, an adequate concentration of penicillin was present in 16, or 80% of 20 determinations. In 9 patients who were given 20,000 units every 2 hours, a level of 0.039 units per cc. or above was found in 51 (67%) of 76 determinations. Following the administration of 15,000 units of penicillin every 2 hours, this same level was obtained in only 29, (63%), out of 46 determinations. There were 25 patients who received 200,000 units of penicillin by continuous intramuscular injections. When the blood was examined at various intervals during the 24-hour period, these therapeutically effective levels were achieved in 142 (96%) of 152 determinations.

TABLE 1.—SERUM PENICILLIN CONCENTRATIONS OBTAINED IN PATIENTS RECEIVING PENICILLIN BY THE CONTINUOUS INTRAMUSCULAR METHOD (200,000 Units of Penicillin Administered in 24 Hours)

Patient	Site of administration	Amount of isotonic saline solution (cc.)	Serum penicillin concentration									
			1 hr.	3 hrs.	6 hrs.	9 hrs.	12 hrs.	18 hrs.	24 hrs.	25 hrs.	26 hrs.	
S. T.	Thigh	2000	.039	.078	.078	.078	.078	.156	.156	.039	.0195	
K. D.	Thigh	2000	.078	.078	.156	.078	.078	.078	.039	0	0	
C. P.	Thigh	2000	.0195	.156	.156	.625	.156	.156	.156	.039	.0195	
R. W.	Thigh	2000	.312	.156	.156	.312	.312	.156	.156	.0195	0	
L. P.	Thigh	2000	.156	.312	.156	.312	.312	.312	.156	.039	.0195	
W. G.	Thigh	2000	.312	.078	.156	.156	.156	.625	.625	.156	.039	
N. B.	Thigh	2000	.078	.078	.078	.156	.156	.078	.078	.0195	0	
J. G.	Thigh	2000	.039	.078	.156	.156	.156	.625	.625	.0195	0	
L. W.	Thigh	2000	.0195	.078	.156	.156	.156	.156	.156	.039	0	
C. P.	Thigh	2000	.039	.156	.156	.312	.312	.156	.156	.039	.0195	
L. P.	Thigh	1000	.078	.156	.078	.078	.078	.156	.078	.0195	0	
S. T.	Thigh	1000	.039	.078	.078	.078	.078	.078	.156	.031	0	
L. D.	Buttock	2000	.078	.078	.078	.078	.078	.156	.156	.039	.0195	
W. B.	Buttock	2000	.039	.039	.039	.078	.078	.078	.156	.0195	0	
J. C.	Thigh	2000*	.039	.039	.039	.039	.078	.078	.156	.0195	0	
C. F.	Thigh	2000 <sup>a</sup>	.078	.078	.039	.039	.156	.156	.156	.078	.0195	
J. M.	Thigh	2000 <sup>a</sup>	.0195	.039	.0195	.039	.039	.156	.156	.078	.0195	
C. S.	Thigh	2000 <sup>b</sup>	.078	.156	.156	.156	.078	.078	.078	.039	.0195	
C. J.†	Thigh	1000	.625	.625	1.25	1.25	1.25	.078	.0195	0	0	
V. G.†	Thigh	1000	1.25	2.5	2.5	2.5	2.5	.039†	0§	0§	0	

\* 4 cc. of 1% neosynephin added. <sup>a</sup> 10 cc. of 1% neosynephin added. <sup>b</sup> 20 cc. of 1% neosynephin added.

† 100,000 units of penicillin administered in 12 hours.

‡ 13-hour level.

§ 14-hour level.

TABLE 2.—COMPARISON OF PENICILLIN CONCENTRATIONS OBTAINED IN THE BLOOD SERUM FOLLOWING INTERMITTENT AND CONTINUOUS INTRAMUSCULAR ADMINISTRATION

200,000 units penicillin in 1000 cc. and 2000 cc. isotonic saline in 24 hours\* by constant intramuscular administration

Penicillin levels (units per cc.)	25,000 units every 3 hrs.		20,000 units every 2 hrs.		15,000 units every 2 hrs.		1 hr.	3 hrs.	6 hrs.	9 hrs.	12 hrs.	18 hrs.	24 hrs.	Other hours		All determinations 3 to 24 hrs. inclusive	1 hr. after termination of drip	2 hrs. after termination of drip
	1 hr.	2 hrs.	3 hrs.	1 hr.	2 hrs.	1 hr.	2 hrs.	1 hr.	3 hrs.	6 hrs.	9 hrs.	12 hrs.	18 hrs.	24 hrs.	hours		of drip	of drip
2.5	0	0	0	0	0	0	0	0	1	1	1	1	0	1	0	4	0	0
1.25	0	0	0	0	0	0	0	1	0	1	1	1	0	0	0	3	0	0
.625	1	0	0	1	0	1	0	1	1	0	1	1	2	0	0	7	0	0
.312	3	0	0	3	0	0	0	2	1	0	3	4	1	0	3	12	0	0
.156	1	2	1	13	2	7	0	1	5	9	5	5	8	9	1	42	1	0
.078	1	1	2	17	5	11	1	6	9	5	7	7	7	4	3	42	2	0
.039	0	2	2	7	3	2	6	6	4	4	3	2	0	2	0	15	10	1
.0195	0	1	3	0	6	1	5	4	0	1	0	0	1	1	3	6	6	7
.009	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
None	0	0	0	0	19	0	11	0	0	0	0	0	0	0	0	0	2	12
No. of determinations	20		76		46		152											
No. of patients	3		9		7		25											

\* Two cases received 100,000 units of penicillin in 1000 cc. isotonic saline in 12 hours.

Figure 1 compares the median concentrations in the serum of patients receiving 200,000 units of penicillin in 24 hours by the continuous intramuscular drip with those receiving 20,000 units every 2 hours by repeated intramuscular injection (or 240,000 units in a 24-hour period). For patients receiving the continuous intramuscular drip, the median serum concentration rose to 0.078 units per cc. at the end of 1 hour. It remained at this level for the next 2 hours, rising to a level of 0.156

COMPARISON OF MEDIAN PENICILLIN SERUM LEVELS  
OBTAINED BY CONTINUOUS INTRAMUSCULAR DRIP AND BY INTERMITTENT INTRAMUSCULAR INJECTIONS

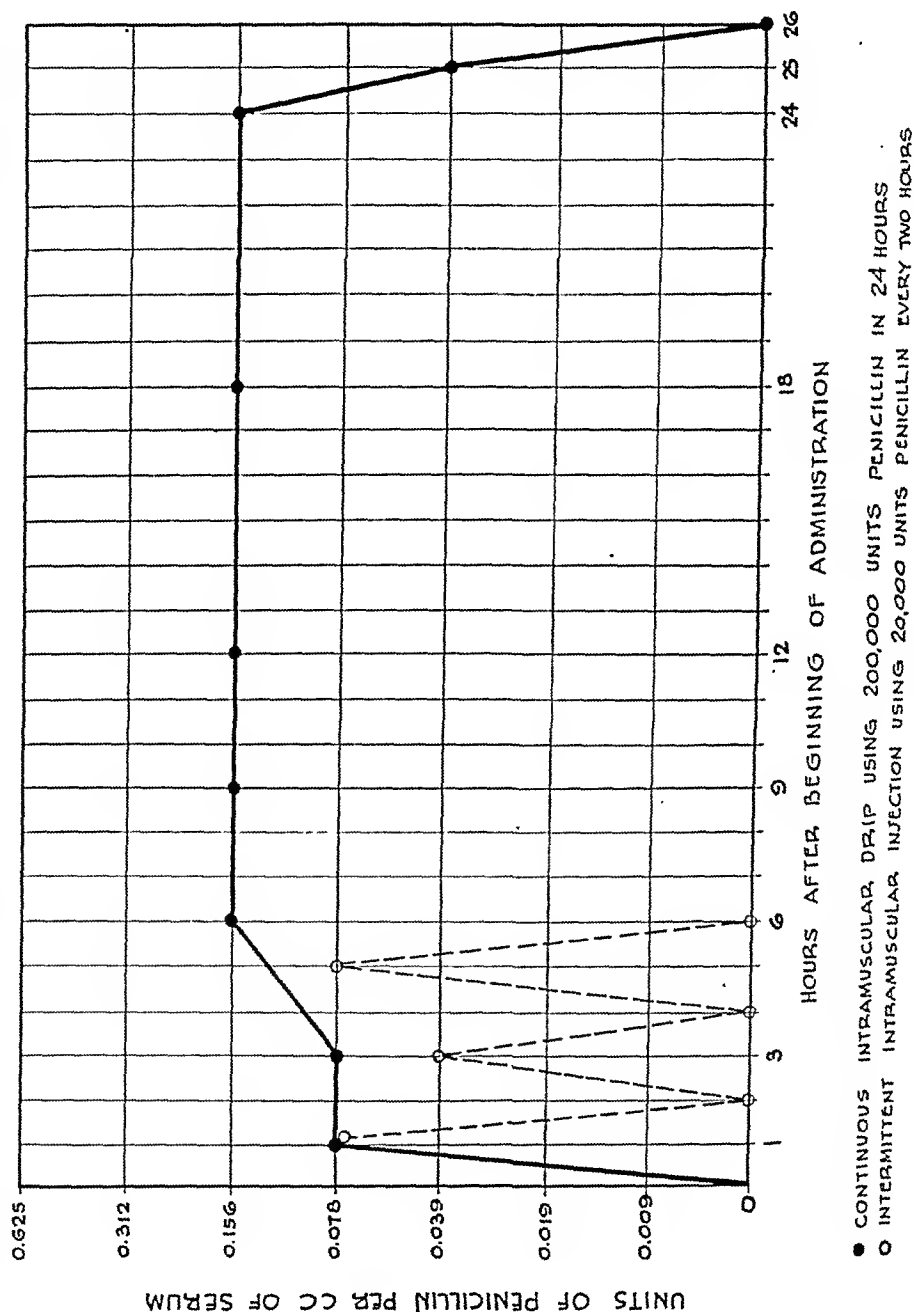


Fig. 1

units per cc. for the remainder of the 24-hour period. The serum level fell to zero within 2 hours after administration was discontinued. This is in marked contrast to the fluctuating median serum levels obtained with doses of 20,000 units every 2 hours. With this method the levels fell from 0.039 or 0.078 units per cc. at the end of 1 hour to zero at the end of 2 hours. The concentrations were determined over a consecutive 6-hour period.

Among the 110 patients to whom we have administered penicillin by the continuous intramuscular method, only 6 complained of mild or moderate discomfort. In 2 of these subjects the pain did not appear until they had received penicillin in one site for several days. When pain at the site of administration did occur, 25 cc. of 1% procaine hydrochloride was added to each liter of solution. This produced prompt and complete relief, so that we were able to continue penicillin administration at the same site as long as treatment was needed, even if this required several additional days. When we added procaine to a penicillin solution *in vitro*, we found that the procaine did not affect the antibacterial activity of the penicillin. Furthermore, the antibacterial activity of serum from patients receiving penicillin together with procaine was no different from the activity of serum from patients receiving penicillin alone.

**Discussion.** We are of the opinion that continuous intramuscular injection is the method of choice for the parenteral administration of penicillin. In a series of 110 cases, we have observed no deleterious effects, except for moderate pain and tenderness at the site of injection in 6 patients. Twenty-five cubic centimeters of 1% procaine added to the solution afforded relief from these discomforts. McAdam and his associates<sup>6</sup> and others<sup>8,12</sup> obviate this difficulty by using only 100 to 600 cc. in a 24-hour period, employing a special apparatus for the administration of these small volumes.

We have found that when the 24-hour dose of penicillin is given in 2 liters of fluid, continuous observation is not necessary in order to insure an even rate of flow, and that pain at the site of injection seldom occurs, especially if the needle is changed to another site every 24 to 96 hours. Thighs and buttocks are both available for these shifts, since we have found that there is no difference in the concentration of penicillin in the serum administered in either of these sites. When a patient does develop pain at the site of injection, the simplest procedure is to add procaine to the solution being administered. This relieves the pain and does not affect the activity of the penicillin.

The obvious advantages of continuous over intermittent intramuscular administration are the achievement of higher continuous serum levels and the elimination of the pain of repeated injections. We have shown that when 8333 units of penicillin are given per hour by the continuous intramuscular method, 96% of the blood penicillin concentrations were therapeutically effective, whereas with intramuscular injections of 25,000 units every 3 hours, only 80% of the concentrations obtained were therapeutically effective. The corresponding figures for the injection of 20,000 and 15,000 units every



2 hours are 67 and 63% respectively. McAdam made similar observations expressing his results slightly differently. He<sup>6</sup> has shown that 6 times as much penicillin is required to maintain a bactericidal level when the drug is given at intervals of 4 hours than when it is given by continuous intramuscular administration; 3 times as much penicillin is required when the interval is 3 hours; and at least  $1\frac{1}{4}$  times as much when the interval is 2 hours. Much nursing time is saved by eliminating the necessity of preparing each penicillin injection. The patient can be allowed almost complete freedom, including bathroom privileges, while receiving the continuous intramuscular drip.

When compared to continuous intravenous administration, the continuous intramuscular method appears superior, obviating the need for good veins, eliminating trauma to the veins and the occurrence of phlebothrombosis. In our hands, similar concentrations in the blood serum were obtained by the continuous intramuscular method when only one-half as much penicillin was used as in the continuous intravenous method. Dawson and Hunter<sup>2</sup> have obtained higher serum levels with the continuous intramuscular than with the continuous intravenous method of administration of the drug.

**Summary and Conclusions.** 1. When penicillin is administered at the rate of 200,000 units in 24 hours (8333 units per hour) by the continuous intramuscular method, the concentration of penicillin in the blood remains constant and at therapeutically effective levels 96% of the time; whereas, with injections of 25,000 units every 3 hours, similar concentrations are obtained only 80% of the time. The corresponding figures for the injection of 20,000 and 15,000 units every 2 hours are 67 and 63%, respectively.

2. There were no deleterious effects or complications in a series of 110 patients in whom this method was employed, except for mild to moderate pain or discomfort at the site of injection in 6 patients. Pain was usually prevented by changing the location of the needle every 24 to 96 hours. When it did occur, it was relieved promptly and completely by the addition of procaine to the penicillin solution.

3. With this method, repeated painful intramuscular or intravenous injections are avoided. The veins of the body are not traumatized and phlebothrombosis is eliminated. The patient has almost complete freedom of activity.

4. The continuous intramuscular drip method is the method of choice for the administration of penicillin to very ill patients who require continuously high concentrations of the drug in the blood.

#### REFERENCES

1. COOKE, J. V., and GOLDRING, D.: The Concentration of Penicillin in Various Body Fluids During Penicillin Therapy, *J. Am. Med. Assn.*, 127, 80, 1945.
2. DAWSON, M. H., and HUNTER, T. H.: The Treatment of Subacute Bacterial Endocarditis With Penicillin, *J. Am. Med. Assn.*, 127, 129, 1945.
3. FLEMING, A., YOUNG, M. Y., SUCHET, J., and ROWE, A. J. E.: Penicillin Content of Blood Serum After Various Doses of Penicillin by Various Routes, *Lancet*, 2, 621, 1944.
4. HARRIS, F. I.: Continuous Intramuscular Infusion of Penicillin, *J. Am. Med. Assn.*, 126, 232, 1944.

5. HERRELL, W. E., NICHOLS, D. R., and HEILMAN, D. H.: Penicillin: Its Usefulness, Limitations, Diffusion, and Detection, With Analysis of 150 Cases in Which It Was Employed, *J. Am. Med. Assn.*, **125**, 1003, 1944.
6. McADAM, I. W. J., DUGUID, J. P., and CHALLINGER, S. W.: Systemic Administration of Penicillin, *Lancet*, **2**, 336, 1944.
7. MORGAN, H. V., CHRISTIE, R. V., and ROXBOROUGH, I. A.: Experiences in the Systemic Administration of Penicillin, *Brit. Med. J.*, **1**, 515, 1944.
8. OSBORNE, C. V.: Intermittent Penicillin Drip Apparatus, *Lancet*, **2**, 407, 1944.
9. RAMMELKAMP, C. H.: A Method of Determining the Concentration of Penicillin in Body Fluids and Exudates, *Proc. Soc. Exp. Biol. and Med.*, **51**, 95, 1942.
10. RAMMELKAMP, C. H., and KEEFER, C. S.: The Absorption, Excretion, and Distribution of Penicillin, *J. Clin. Invest.*, **22**, 425, 1943.
11. RANTZ, L. A., and KIRBY, W. M. M.: The Absorption and Excretion of Penicillin Following Continuous Intravenous and Subcutaneous Administration, *J. Clin. Invest.*, **23**, 789, 1944.
12. ST. HILL, C. A.: Apparatus for Systemic Administration of Penicillin to Young Children, *Brit. Med. J.*, **1**, 631, 1944.

## ELECTROCARDIOGRAPHIC OBSERVATIONS IN NORMAL THYROIDECTOMIZED AND THIOUREA TREATED RATS\*

BY ROBERT K. WALLER

RESEARCH ASSISTANT, ORTHORESEARCH FOUNDATION, LINDEN, N. J.

AND

HARRY A. CHARIPPER

PROFESSOR OF BIOLOGY, GRADUATE SCHOOL OF ARTS AND SCIENCE  
NEW YORK UNIVERSITY, NEW YORK, N. Y.

With the Technical Assistance of MR. ALBERT H. STENGER

THE literature on the use of the electrocardiograph on small laboratory animals, such as mice and rats, is extremely sparse.

Agduhr and Stenström<sup>1</sup> investigated electrocardiographic changes in mice after cod-liver oil treatment. A string galvanometer built for human use with a string speed of 0.01 second was used in this work. Small zinc plates, amalgamated with mercury and wrapped in cotton soaked in physiologic NaCl solution were used as electrodes. The standardization was 1 mv. per centimeter. An attempt was made to establish the normal mouse electrocardiogram using a small number of animals. The average heart rate was found to be 560 per minute with a conduction time varying between 0.025 and 0.045 second. The authors also stated that arrhythmias and extremely low deflections in Lead I were commonly found, and that there were changes in the electrical axis of the same animal on repeated examinations.

The most characteristic statement concerning the findings of Agduhr and Stenström, indicating the inadequacy of the apparatus used, is, "A feature generally met with in the electrocardiograph of mice is that the summits of the T waves can almost never be discovered, which seems noteworthy inasmuch as the other deflections are sometimes nearly as large as those of the human electrocardiogram. Instead of an independent T summit, there appears however, with great

\* This report contains material accepted in partial fulfillment of the requirements for the degree of Master of Science, New York University.

consistency, terminating the QRS complex, a slow return of the string to the isoelectric line . . . ."

Weiss, Haynes, and Zoll<sup>11</sup> studied electrocardiographic changes in vitamin deficient rats and in 7 normal rats. The main deflections were found to be upright in all leads with extremely low deflections in Lead 1. The average voltage of the main deflection in Lead 2 ( $R_2$ ) was stated to vary between 0.8 and 0.2 mv. The average height of  $T_2$  ranged from 0.25 to 0.05 mv. The statement characteristic of the inadequacy of the galvanometer used in this investigation is, that the origin of all T waves was found to be elevated. This fact is also amply illustrated by graphs shown by the authors.

Griffith<sup>5</sup> in his textbook simply stated that electrocardiograms can be taken in rats by means of a string galvanometer and needle electrodes, and showed a graph of Lead 2.

Rappaport and Rappaport<sup>10</sup> pointed out for the first time, the complete inability of string galvanometers alone, and also commercial amplifier electrocardiographs, to register correctly the electrocardiographic pattern of any animal with a heart rate essentially higher than that of man. The slow string speed or the high inertia of the mirror galvanometer used causes superimposition of deflections with consequent graphic distortion. In order to overcome these difficulties, the authors recommended the use of a resistance coupled amplifier in conjunction with a string galvanometer with high vibration speed.

The primary purposes of this investigation are to establish, with the use of this recently recommended equipment, first, an average pattern of an electrocardiogram for the normal rat; and secondly, to study such electrocardiographic changes which may be produced by thyroidectomy and compare them with changes following treatment with thiourea.

**Material and Methods.** In order to establish an average electrocardiographic pattern, 24 male and 26 female hooded albino rats were used. Their weights ranged from 107 to 360 gm. Out of these 50 rats, 8 were thyroidectomized and 8 were subjected to 1% thiourea in drinking water. The electrocardiograms of the thyroidectomized animals were repeated after 1 month, as were those of the thiourea treated animals after 3 weeks. Also used in this study were 2 male rats which had been thyroidectomized 6 months previously.\*

For the purpose of electrocardiography, all animals were anesthetized with intraperitoneal injections of 30 mg. of nembutal per kg. of body weight, and subsequently permitted to rest for at least 15 minutes. The recording instrument used was a commercial string galvanometer electrocardiograph together with the electronic amplifier (Fig. 1) recommended by Rappaport and Rappaport.<sup>10†</sup>

Because of alternating current interference it was necessary to place the animal into a wire cage, grounded together with amplifier and galvanometer. To reduce interference further, a 0.1 mfd condenser was placed into the main ground wire through which the three parts of the apparatus were then grounded. The 3 lead wires of the amplifier were then connected to the animal by thrusting 26-gauge hypodermic needles attached to these wires, beneath the skin of the left and right foreleg and left hindleg for a distance of 1 cm. In order

\* Supplied by Dr. A. S. Gordon.

† Acknowledgment with thanks is hereby made to the Flushing Hospital for use of the electrocardiograph.

to reduce further any disturbing AC interference, it was essential to rub the fur of the legs with electrode jelly before applying the electrodes. Through this procedure, the electrode-skin resistance was reduced, thereby eliminating another possible pick-up of extraneous currents.

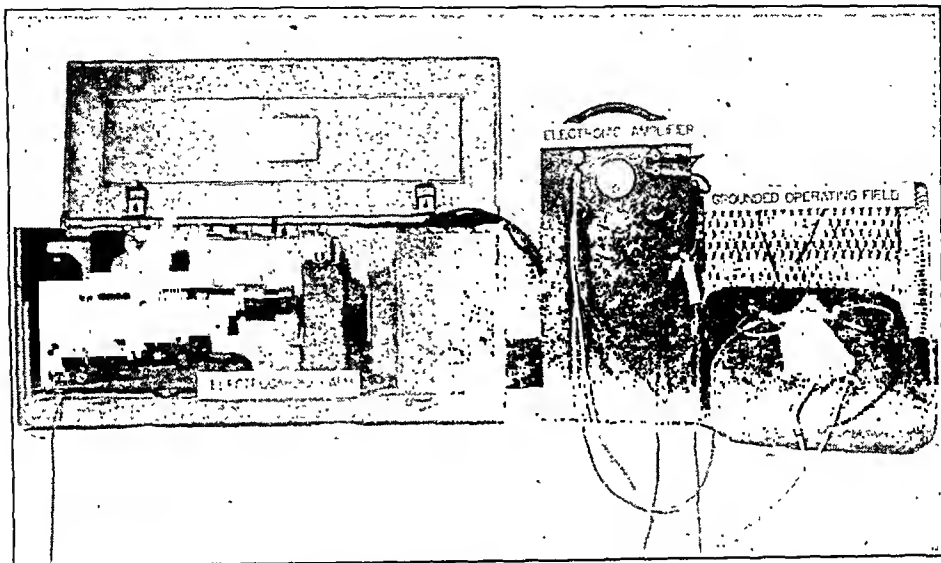


FIG. 1.—Electrocardiograph with electronic amplifier in position for use.

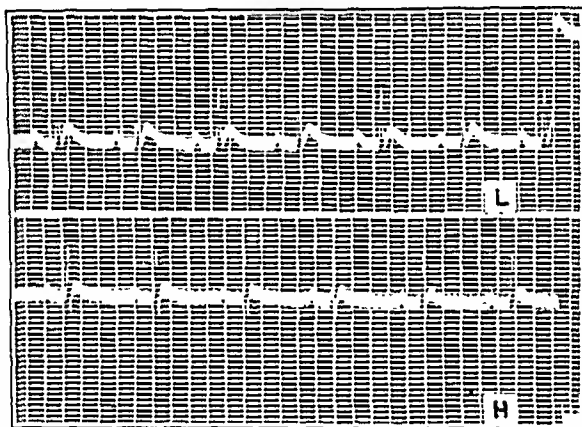


FIG. 2.—Electrocardiogram taken with low (L) and high (H) string speeds respectively (Lead 2).

The standardization used in this investigation was 20 mm. per millivolt. The recording speed was 75 mm. per second, *i. e.*, 3 times normal speed.

In order to demonstrate the difference in appearance in a rat electrocardiogram taken with low and high string speed, Figure 2 is shown.

Both graphs were taken in Lead 2 position on the same animal. The upper one was recorded by means of a commercial string galvanometer electrocardiograph. This graph shows clearly the superimposition of the T waves upon the terminal part of the QRS complexes. The take-off of the T waves is markedly elevated. S waves are minimal. The lower graph, taken with the same instrument but in conjunction with the amplifier and high string tension,

shows the take-off of the ST segments to be in the isoelectric line and the presence of a well formed S wave. The increase of deformities with increased heart rate was well demonstrated by the graphs of white mice shown in the publication of Rappaport and Rappaport.<sup>10</sup>

**Experimental Results.** A. *Analysis of Electrocardiograms on Normal Rats.* The average pattern of a normal rat electrocardiogram was established from calculations of 50 graphs taken on 50 individual animals. Because the amplitude of the QRS complexes in Leads 1 and 3 is greatly affected by changes of the electrical axis and because of Einthoven's law, only amplitudes of the waves in Lead 2 were used for the detection of electrocardiographic changes.

The mean measurements of the different components with their deviations from the mean and their range is shown in Table 1.

TABLE 1.—MEASUREMENTS OF COMPONENTS OF THE ELECTROCARDIOGRAPHIC COMPLEX IN 50 ANIMALS

	Mean	Range
Weight of animals . . . .	189 gm. $\pm$ 53	360-107
Heart rate . . . . .	328 $\pm$ 17 per min.	360-261
P-R interval (conduction time)	0.047 sec. $\pm$ 0.002	0.053-0.038
Height of R <sub>2</sub> waves . . . .	0.463 mv. $\pm$ 0.097	0.750-0.300
Height of T <sub>2</sub> waves . . . .	0.106 mv. $\pm$ 0.029	0.225-0.050

In this table a remarkably wide range of measurements can be seen, which however, is thoroughly comparable to the wide range of normal values observed in humans. The sexes were equally distributed in this series and no sex linked variations could be observed throughout the study.

The distribution of axis deviation in this series is shown in Table 2.

TABLE 2.—DISTRIBUTION OF AXIS DEVIATION

Axis deviation	No. of rats
Left . . . . .	8
Tendency to left . . . . .	6
None . . . . .	27
Tendency to right . . . . .	9
Right . . . . .	0

Thus, slightly more than half of the animals showed no axis deviation at all; approximately 28% showed deviation to the left; and only 18% showed a tendency to right axis deviation. Frank right axis deviation was never observed.

In order to determine the influence of animal weight upon axis deviation, Table 3 was drawn up.

TABLE 3.—AXIS DEVIATION ACCORDING TO WEIGHT OF RAT

Animal weight (gm.)	Left	Tendency to left	None	Tendency to right	Right
100-150 . . . . .	1	1	7	6	0
151-200 . . . . .	5	2	8	2	0
201-250 . . . . .	3	0	5	1	0
251-300 . . . . .	1	0	4	0	0
301-360 . . . . .	1	0	3	0	0

This table shows the preponderance of "tendency to right" over "tendency to left" in the lower weight group, which diminishes and finally disappears completely in the higher weight groups.

These results are not dissimilar to those reported by Weiss *et al.*,<sup>11</sup> although in this series, all waves are somewhat lower because of lack of superimposition of deflections. The general outline of the complexes is identical with those of the human electrocardiogram. The deflections in Lead 1 were found to be very low in the majority of animals, a phenomenon which can easily be explained by the relative center position of the rat heart in the first lead, and by the relative shortness of this lead as compared to the remainder of the standard leads. Deflections of Lead 3 were found to be usually well formed but somewhat lower than those seen in Lead 2. All ST segments were found to be isoelectric and not elevated as shown by other authors. Well formed S waves were found in the majority of Leads 2 and 3.

B. *Analysis of Electrocardiograms on Thyroidectomized Animals.* The electrocardiographic effects of thyroidectomy of 4 weeks standing are shown in Table 4. All animals were thyroidectomized immediately after the first electrocardiogram and rechecked after 1 month. Also included in this table are 2 rats with thyroidectomies of 6 months standing. Attention should be called to the fact that Rat 6 was only hemi-thyroidectomized because of excessive bleeding.

In order to avoid any misinterpretation of changes in the amplitude of R waves which could be accounted for by the absence or occurrence of a prominent S wave, the total amplitude of the QRS complex was measured and tabulated in millimeters. Although it is customary to express all amplitudes in millivolts, this was avoided in this instance, because R waves are positive in direction whereas S waves are negative. Their algebraic sum is therefore less indicative of any change than their geometric sum (R+S).

TABLE 4.—EFFECTS OF THYROIDECTOMY

Sex and animal No.	Time since thyx.	Wt.	Heart rate per m.	P-R interval (sec.)	R <sub>2</sub> (mv.)	Total amplitude R + S (mm.) (Lead 2)	T <sub>2</sub> (mv.)	Axis deviation
♀ 1	0	139	355	0.045	0.750	19.0	0.113	Tend. rt.
1 R*	1 mo.	185	344	0.046	0.500	14.0	0.075	Tend. rt.
♂ 2	0	137	351	0.038	0.675	15.0	0.125	None
2 R	1 mo.	170	336	0.042	0.500	14.0	0.100	Tend. rt.
♂ 4	0	140	348	0.043	0.388	16.0	0.175	Tend. rt.
4 R	1 mo.	185	324	0.054	0.350	13.5	0.055	Tend. lt.
♂ 6	0	125	324	0.048	0.445	12.5	Isoel.	Tend. rt.
6 R	1 mo.	128	354	0.049	0.500	12.5	0.063	Tend. lt.
♂ 8	0	171	360	0.044	0.425	12.5	0.163	None
8 R	1 mo.	238	348	0.046	0.325	10.0	0.100	Tend. rt.
♀ 9	0	162	339	0.042	0.750	19.5	0.138	None
9 R	1 mo.	172	330	0.045	0.563	14.5	0.113	Tend. rt.
♀ 10	0	202	357	0.046	0.355	12.0	0.105	Tend. rt.
10 R	1 mo.	248	333	0.048	0.205	9.0	0.025	Tend. lt.
♂ 22	0	163	330	0.047	0.450	13.0	0.088	None
22 R	1 mo.	210	330	0.047	0.388	12.0	0.063	None
♂ 53	6 mos.	327	300	0.050	0.325	12.5	0.100	Tend. lt.
54	6 mos.	271	258	0.064	0.275	7.5	-0.063	Tend. rt.

\* The letter R after the animal number indicates a repeat electrocardiogram on the same animal after the time interval stated in the second column.

This table shows that in 6 of 7 animals, disregarding Rat 6, there was a small weight gain, a drop in heart rate, and a concomitant widening of the P-R interval. The voltage of the R waves also decreased in these animals as did the total amplitude of the QRS complex (R+S). There was also a definite lowering of all T waves. Although there was a change of axis deviation in the majority of animals, no definite trend toward any direction could be made out. Of the 2 animals thyroidectomized 6 months previously, 1 showed a heart rate somewhat lower, the other a heart rate markedly lower than that observed after 1 month of thyroidectomy. The conduction time of these animals was correspondingly lengthened and all positive waves were found to be lower than their corresponding means.

*C. Analysis of Electrocardiographs on Thiourea Treated Animals.* The electrocardiographic changes effected by the administration of 1% thiourea in drinking water for a period of 3 weeks are compiled in Table 5.

TABLE 5.—EFFECTS OF THIOUREA (1% IN DRINKING WATER)

Sex and animal No.	Time of treat.	Wt.	Heart rate per m.	P-R interval (sec.)	R <sub>2</sub> (mv.)	Total amplitude R + S (mm.) (Lead 2)	T <sub>2</sub> (mv.)	Axis deviation
♀ 12	0	107	321	0.048	0.488	16.0	0.200	Tend. rt.
12 R	3 wks.	93	222	0.063	0.575	18.5	0.100	Tend. rt.
♀ 13	0	116	333	0.044	0.513	14.0	0.150	None
13 R	3 wks.	100	279	0.048	0.575	15.0	0.075	Tend. rt.
♂ 14	0	134	327	0.044	0.475	14.0	0.163	None
14 R	3 wks.	102	228	0.059	0.600	17.5	0.075	Tend. rt.
♂ 16	0	158	345	0.046	0.613	16.5	0.088	Tend. lt.
16 R	3 wks.	115	285	0.058	0.650	18.0	0.050	None
♂ 17	0	147	354	0.046	0.538	14.0	0.150	None
17 R	3 wks.	137	210	0.064	0.538	14.0	0.075	Tend. rt.
♀ 18	0	110	261	0.054	0.712	17.0	0.138	Tend. rt.
18 R	3 wks.	102	162	0.064	0.763	18.0	0.050	Tend. rt.
♀ 19	0	113	306	0.046	0.650	18.0	0.025	None
19 R	3 wks.	104	206	0.050	0.550	18.0	Isocl.	Tend. rt.
♀ 20	0	118	345	0.045	0.550	14.5	0.150	None
20 R	3 wks.	85	210	0.059	0.563	16.5	0.100	Tend. rt.

All 8 animals lost weight during the treatment. Their heart rate was reduced to approximately two-thirds of the original value, accompanied by a corresponding lengthening of the conduction time. In striking contrast to the thyroidectomized animals, these animals showed an increase of voltage in R<sub>2</sub>, 6 times out of 8. This was borne out by a parallel increase in total QRS amplitude (R+S). The T waves showed a drop of voltage in all cases, much more drastic than that seen in thyroidectomized animals. Six animals out of 8 showed a definite shift of the electrical axis to the right, whereas 2 retained their original axis deviation.

**Discussion.** In order to demonstrate more clearly the electrocardiographic changes appearing after thyroidectomy, the graphs of representative animals before and after thyroidectomy are shown in Figure 3.

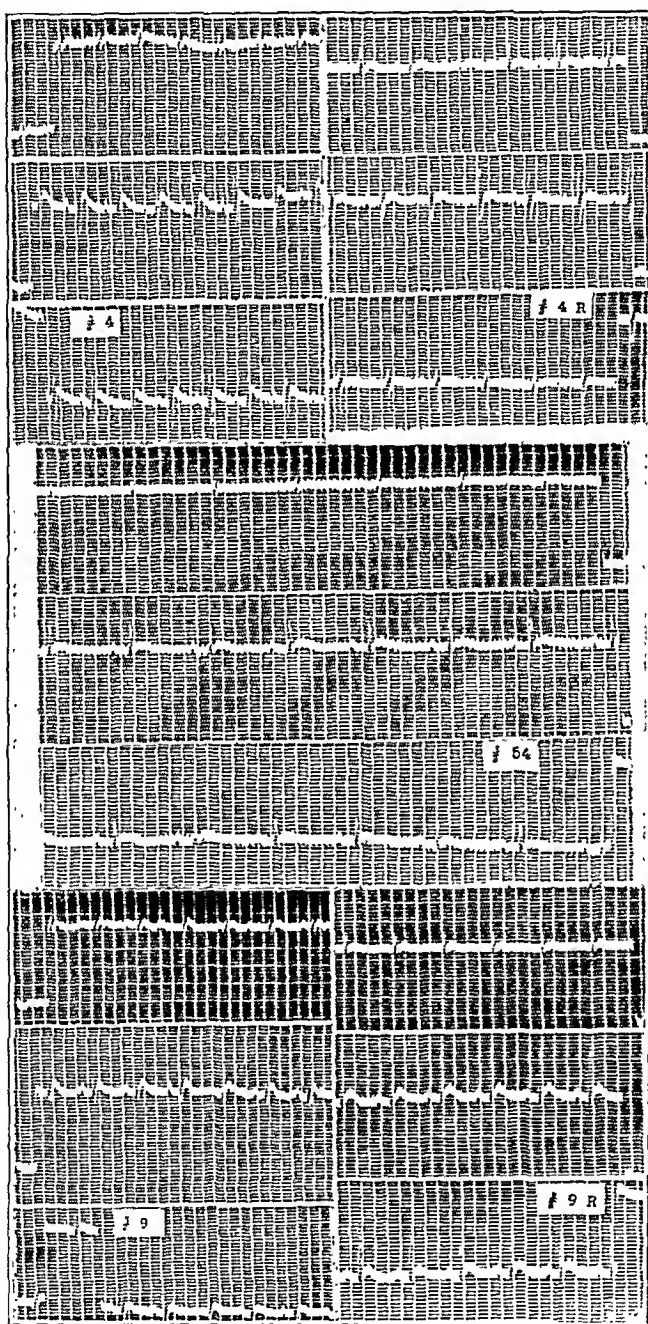


FIG. 3.—Electrocardiogram of animals before (Nos. 4, 9) and after (Nos. 4 R, 54, 9 R) thyroidectomy.



A general trend toward the slowing and lowering of all complexes can easily be seen. These graphs also serve to illustrate the inconsistency of changes of the electrical axis, as Rat 4 changed to the left, whereas Rat 9 changed to the right after thyroidectomy. The trend of the changes concerning heart rate and height of deflection is in full accord with myxedematous changes seen in human electrocardiograms.<sup>2,4,6</sup> As can be seen from graph No. 54 (Fig. 3), taken 6 months after thyroidectomy, there are extremely low-voltage QRS complexes with isoelectric T waves in Leads 2 and 3.

The slowing of the heart rate and the lowering of all complexes in cases of myxedema, are said, by some authors, to be due to a hydro-pericardium which however, could not be observed at autopsy of the 2 long-time thyroidectomized animals. The other, more likely, point of view is that these changes are produced by interstitial edema of the cardiac muscle, which would certainly tend to change its conductivity.<sup>6</sup>

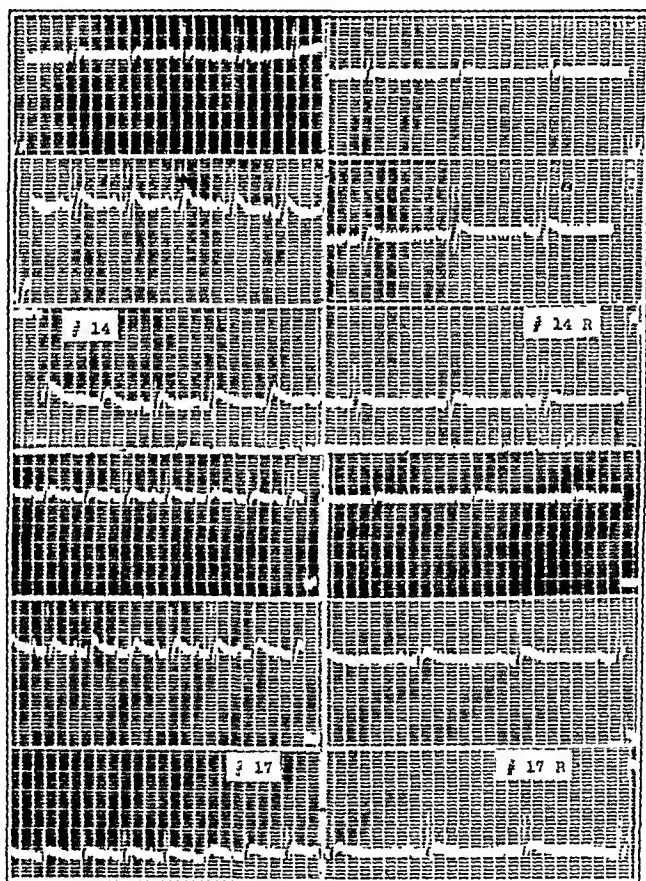


FIG. 4.—Electrocardiogram of animals before (Nos. 14, 17) and after (Nos. 14 R, 17 R) thiourea treatment.

The electrocardiographic changes following treatment with 1% thiourea for 3 weeks are illustrated by graphs No. 14 and 17, Figure 4.

Here, as in the case of the thyroidectomized animals, there is a decrease in heart rate; however, it is found to be much more pronounced after thiourea despite the fact that these animals had only been treated for 3 weeks. The conduction time shows a parallel increase and the T waves are found to be markedly lowered. These, like the majority of electrocardiograms after thiourea treatment show a decided change of the electrical axis to the right.

In complete contrast to the thyroidectomized animals, there is an increase in voltage of the R waves together with an increase of the total amplitude of the QRS complex (R+S).

It is well to remember however, that the decrease in amplitude of the ventricular complexes is an integral part of the "myxedema electrocardiogram."<sup>2,4,6,7</sup>

In order to illustrate the partial parallelism and the marked partial discrepancy of electrocardiographic changes after thyroidectomy and after thiourea treatment, Table 6 was drawn up.

TABLE 6.—ELECTROCARDIOGRAPHIC CHANGES

	After thyroidectomy	After thiourea
Weight of rat . . . .	+31.2 $\pm$ 18	-20 $\pm$ 11.3
Heart rate . . . . .	-11.8 $\pm$ 6.1	-98 $\pm$ 21.2
P-R interval . . . . .	+0.003 $\pm$ 0.002	+0.012 $\pm$ 0.004
R <sub>2</sub> . . . . .	-0.137 $\pm$ 0.060	+0.034 $\pm$ 0.039
R + S . . . . .	-2.9 $\pm$ 1.2	+1.6 $\pm$ 0.66
T <sub>2</sub> . . . . .	-0.054 $\pm$ 0.029	-0.092 $\pm$ 0.035

In this table the mean changes with their direction and deviation from the mean are recorded for each procedure.

Whereas thyroidectomized animals gained weight during the interval of 1 month, all thiourea treated animals lost weight. There was a drop in heart rate with increased conduction time after both procedures, which was however more marked after thiourea treatment. The R waves and the total amplitude of the ventricular complex (R+S) lost in voltage significantly after thyroidectomy, whereas the opposite could be observed after thiourea treatment. Finally, there was a characteristic drop in amplitude of the T waves after both procedures.

Although thyroidectomy produces electrocardiographic changes similar, if not identical, with those seen in human cases of myxedema, thiourea treatment duplicates this disease electrocardiographically only to a limited extent. This observation is in contrast to the views of Leblond and Hoff<sup>7,8</sup> who stated that 1% thiourea in drinking water given to rats produces cardiac changes equal in degree to those produced by thyroidectomy.

The difference in reaction to the two procedures could possibly be explained by a direct toxic action of thiourea on the body and on the heart in particular. This view would be partially supported by the fact that the animals lost weight during treatment. Another explanation would be that thyroxin is formed outside of the thyroid gland, a view previously expressed by Chapman<sup>3</sup> and Morton *et al.*<sup>9</sup>

Although the latter view would account for the comparatively greater severity and speed with which changes occur after thiourea

treatment, it would not account for the comparative increase in amplitude of the QRS complexes, which still remain unexplained.

**Summary and Conclusions.** 1. The average appearance of a rat electrocardiogram was established from the analysis of 50 graphs recorded by means of a string galvanometer with high vibration speed in conjunction with an electronic amplifier.

The mean heart rate was found to be 328 beats per minute, with a corresponding mean conduction time of 0.047 second.

The mean amplitude of the R waves in Lead 2 was found to be 0.463 millivolts, the mean voltage of  $T_2$  0.106 millivolt.

The ranges of these measurements were found to be fairly wide and entirely unrelated to sex and age of the animals. The majority of graphs showed no axis deviation. There was a slight preponderance of a "tendency to the right" over "tendency to the left" in the lower weight groups, which however decreased on approaching the higher weight groups.

2. Electrocardiograms were studied on thyroidectomized animals and animals treated with 1% thiourea in drinking water.

The changes after thyroidectomy simulated in all respects changes seen in human cases of myxedema, *i. e.*, lowering of heart rate with increased conduction time and lessened amplitude of all positive waves. Animals, 3 weeks after thyroidectomy, showed these changes to a lesser extent than those thyroidectomized 6 months previously.

Treatment of normal rats with thiourea for a period of 3 weeks produced marked slowing of the heart rate with increased conduction time and lowered amplitudes of the T waves. However, there was a striking tendency to increase the voltage of the R waves in complete contrast to the expected myxedematous changes.

Although there was no consistent shift in axis deviation after thyroidectomy, there was a definite shift to the right in the majority of thiourea treated animals.

3. The more complete myxedema-like response obtained after thiourea treatment as compared to that elicited following thyroidectomy lends further substantiation to the extra-thyroidal production of thyroxin as proposed by Chapman<sup>3</sup> and Morton *et al.*<sup>9</sup>

#### REFERENCES

1. AGDUHR, E., and STENSTRÖM, N.: *Acta pædiat.*, 8, 493, 1929.
2. ASHMAN, R., and HULL, E.: *Essentials of Electrocardiography*, New York, Macmillan, 1941.
3. CHAPMAN, A.: *Endocrinology*, 29, 686, 1941.
4. GRAYBIEL, A., and WHITE, P. D.: *Electrocardiography in Practice*, Philadelphia, W. B. Saunders, 1941.
5. GRIFFITH, J. A., and FARRIS, E. J.: *The Rat in Laboratory Investigation*, Philadelphia, Lippincott, 1942.
6. LANGE, K.: *Am. J. Med. Sci.*, 208, 5, 1944.
7. LEBLOND, C. P., and HOFF, H. E.: *Am. J. Physiol.*, 141, 32, 1944.
8. LEBLOND, C. P., and HOFF, H. E.: *Endocrinology*, 35, 229, 1944.
9. MORTON, M. E., *et al.*: *J. Biol. Chem.*, 147, 757, 1943.
10. RAPPAPORT, M. B., and RAPPAPORT, I.: *Am. Heart J.*, 26, 662, 1943.
11. WEISS, S., *et al.*: *Am. Heart J.*, 15, 206, 1938.

# A STUDY OF THE RELATIONSHIP OF THE BASAL BODY TEMPERATURE TO THE BASAL METABOLIC RATE IN HOSPITALIZED PATIENTS

BY CAMPBELL MOSES, M.D.

PITTSBURGH, PA.

(From the Department of Physiology and Pharmacology and the Presbyterian and Elizabeth Steel Magee Hospitals of the University of Pittsburgh)

THE recent recommendation of the use of the basal body temperature in determining the time of ovulation<sup>2,3,5,7,11,13,14,15,16</sup> and the renewed clinical interest in the relationship of the body temperature

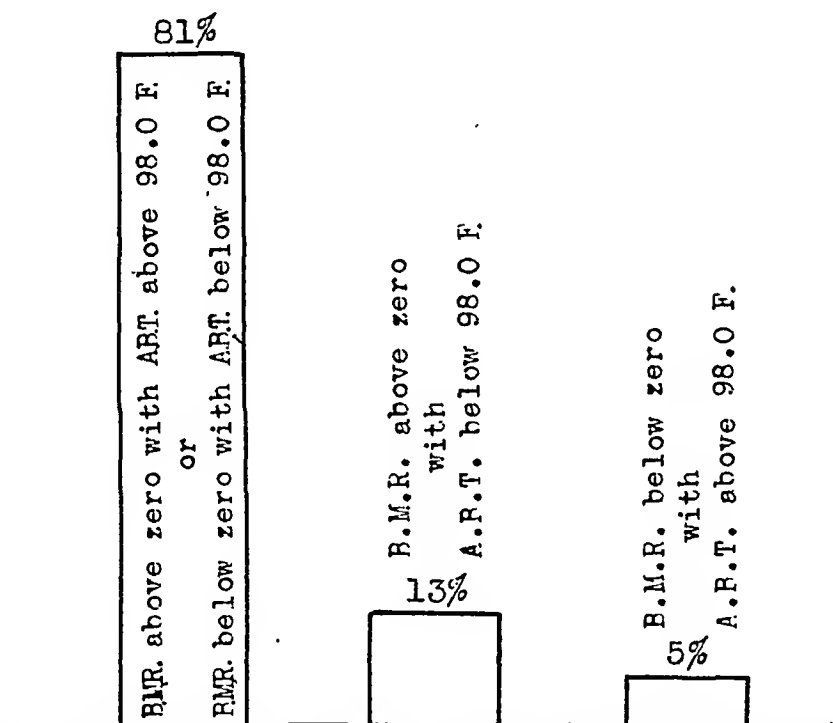
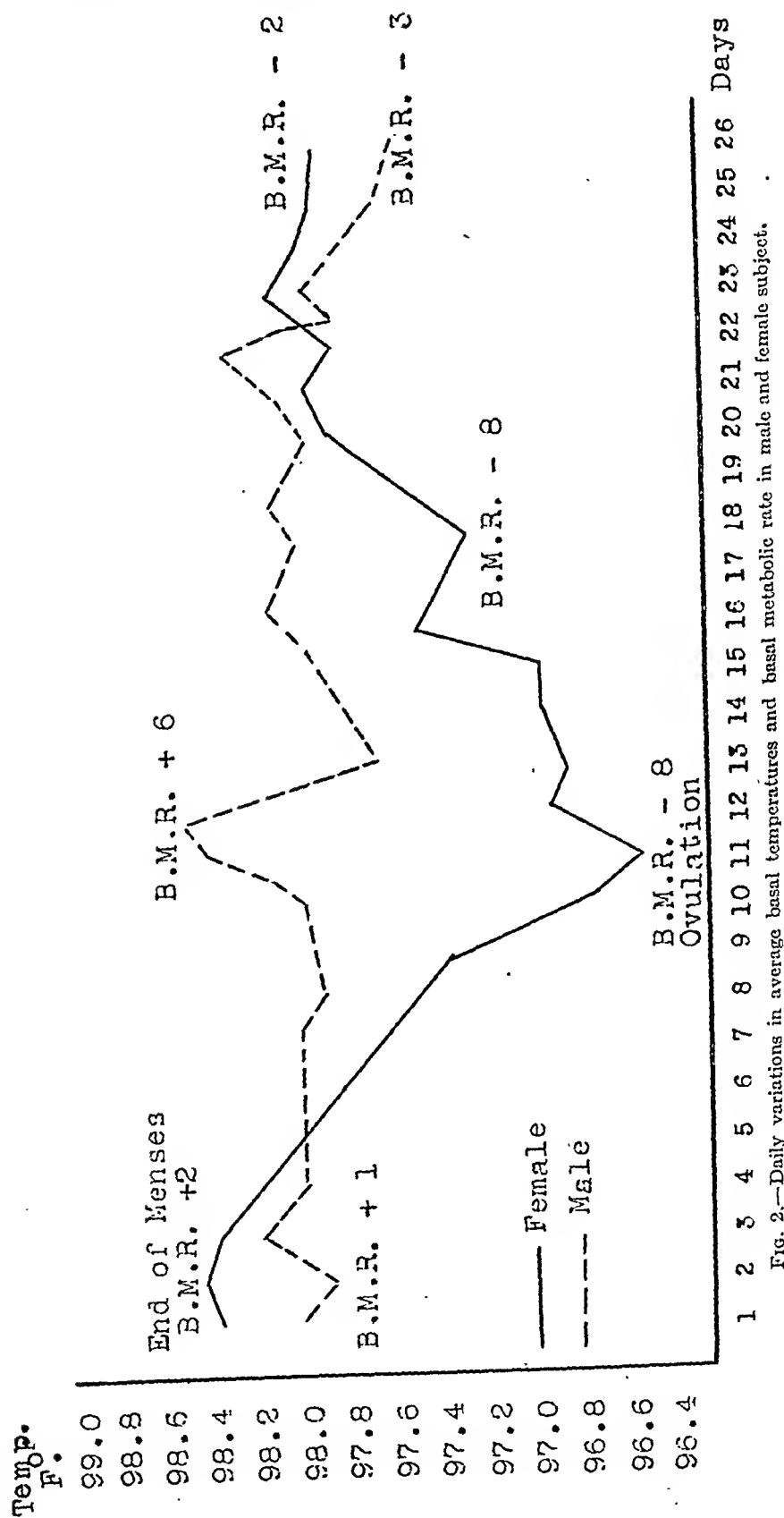


FIG. 1.—Relationship between the basal metabolic rate (B.M.R.) and the average basal temperature (A.B.T.) in 255 Hospital Patients.

to the basal metabolic rate<sup>1,6,8,12,14,16</sup> occasioned this study. If, as has been suggested,<sup>1</sup> the basal body temperature is a better index for thyroid therapy than the basal metabolic rate, this is of particular importance now in industrial centers where patients cannot take time off from vital war work for determinations of the basal metabolic rate. The use of basal temperature graphs in timing the course of events in the human menstrual cycle apparently rests on adequate clinical and experimental evidence.<sup>5,7,11,15</sup> However, the evidence supporting an exact correlation between the average basal temperature and the basal metabolic rate requires additional consideration.



The work here reported was undertaken to determine what correlation, if any, exists in the afebrile hospital patient between the average basal temperature and the basal metabolic rate.

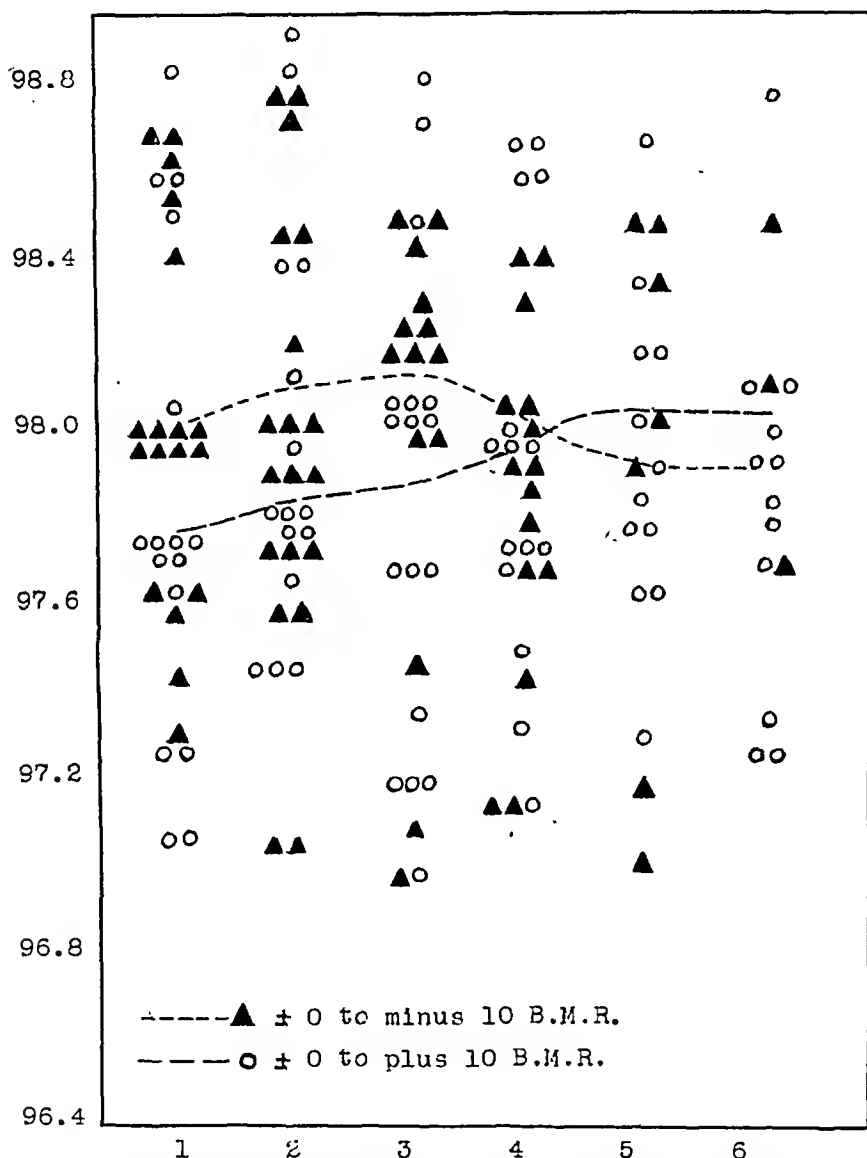


FIG. 3.—The wide variation in the basal temperature readings of individuals with +10 to -10 B.M.R. and the average basal temperature of these subjects.

**Procedure.** To determine this, the hospital records of individuals admitted for diagnostic investigation were reviewed.\* Patients with febrile conditions were not included. The basal temperature determinations were taken as the early morning (7 to 8 A.M.) oral temperatures before the patient had been out of bed. The routinely determined metabolic rates were utilized. These were usually performed in duplicate or until consecutive determinations agreed satisfactorily.

In all, 255 patients were studied, 1150 basal temperature determina-

\* Through the courtesy of Drs. A. H. Colwell, F. J. Gregg, and J. W. Shirer.

tions being made on the members of the group. Arbitrarily 98° F. was chosen as the normal basal temperature. Using this figure as normal, there was general agreement between the basal metabolic rate and the average basal temperature in 208 of the 255 patients

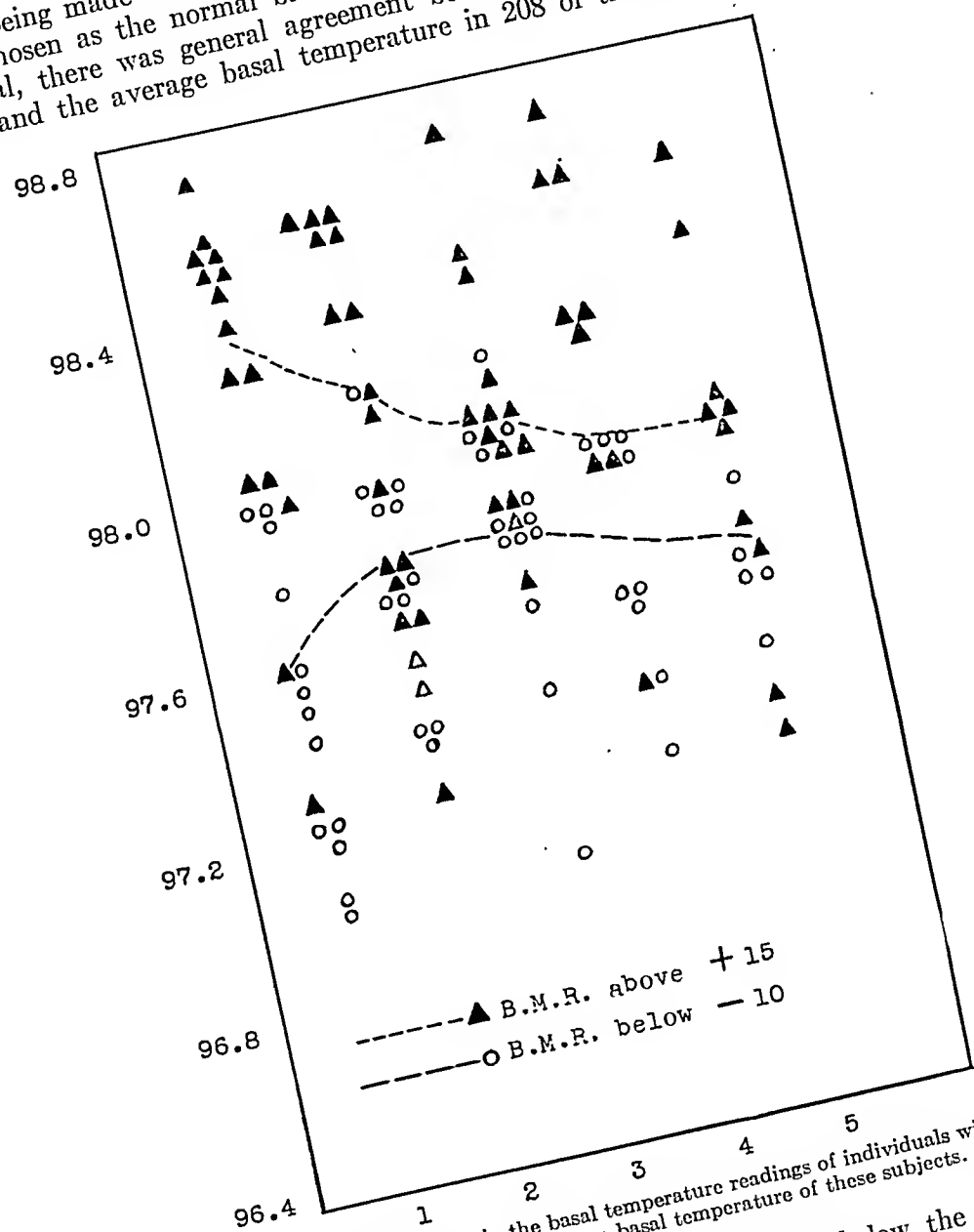


FIG. 4.—The wide variations in the basal temperature readings of individuals with high and low B.M.R. and the average basal temperature of these subjects.

(81%); i. e., if the basal metabolic rate was zero or below, the average basal temperature was 98° F. or below (46%); or if the basal metabolic rate was zero or above, the average basal temperature was 98° F. or above (35%). In 34 patients (13%) the metabolic rate was above zero, although the average basal temperature was below 98° F. In 13 patients (5%) the basal temperature was above 98° F. with a negative basal metabolic rate. Figure 1 summarizes these findings.

The relatively high degree (81%) of agreement between the basal metabolic rate and the average basal temperature conforms to the well founded clinical observation that individuals with elevated metabolic rates generally have higher body temperatures (Fig. 4) and, indeed a low grade fever is frequently seen in thyrotoxicosis.<sup>4</sup> Similarly hypothyroidism in both man and animals is often accompanied by a relatively low average basal temperature.<sup>4,8,12</sup> However, it must be recognized that, while general agreement between the average basal temperature and the basal metabolic rate obtains, this generalization does not necessarily indicate that the average basal temperature can replace determinations of the basal metabolic rate.

Two reasons for this are apparent: (a) while in the normal male there is relatively little cyclic fluctuation in temperature, in the female the temperature variations due to hormonal activity are quite marked (Fig. 2) and, although these temperature variations are accompanied by a somewhat similar change in basal metabolic rate the two changes are not of strictly comparable magnitude;<sup>14</sup> (b) the second reason for the inability of the average basal temperature to be substituted for the basal metabolic rate is the tremendous overlapping that obtains both in the relatively normal group ( $\approx 10\%$  B.M.R.) and those with definitely abnormal metabolic rates. Study of Figures 3 and 4 emphasizes the wide variations in basal temperature and indicates the difficulty encountered in attempting to give the average basal temperature the same significance as the basal metabolic rate. Although the temperature curve tends generally to be higher in the hyperthyroid individual and lower in the hypothyroid, this is not an invariable finding and there is a great deal of overlapping between the two groups. Study of Figure 4 indicates that while individuals with a high B.M.R. may have low basal temperatures, those with low B.M.R. seldom have basal temperatures above 98° F.

**Summary and Conclusions.** Evidence is presented to indicate that while the average basal temperature and the basal metabolic rate are in general agreement, individual determinations of the basal metabolic rate cannot be replaced by average basal temperatures in estimating the degree of metabolic activity.

#### REFERENCES

1. BARNES, B.: J. Am. Med. Assn., **119**, 1072, 1942.
2. BARTON, D. S.: Yale J. Biol. and Med., **12**, 503, 1940.
3. D'AMOUR, F. E.: J. Clin. Endocrinol., **3**, 41, 1943.
4. DuBois, E. F.: Basal Metabolism in Health and Disease, Philadelphia, Lea & Febiger, 1936.
5. GREULICH, W., and MORRIS, E. S.: Anat. Rec., **79**, 27, 1941.
6. GRIFFITH, F. R., JR., PUCHER, G. W., BROWNELL, K. A., KLEIN, J. D., and CARMER, M. E.: Am. J. Physiol., **87**, 602, 1929.
7. HARVEY, O. L., and CROCKETT, H. E.: Human Biol., **4**, 453, 1932.
8. KORENCHESKY, V.: J. Path. and Baet., **29**, 461, 1926.
9. LYON, D. M., and WALLACE, H. L.: Brit. Med. J., **1**, 980, 1932.
10. LYON, R. A.: Surg., Gynec. and Obst., **76**, 729, 1943.
11. MARTIN, P. L.: Am. J. Obst. and Gynec., **46**, 53, 1943.
12. MURRAY, G. R.: Brit. Med. J., **1**, 359, 1920.
13. PALMER, A.: Surg., Gynec. and Obst., **75**, 768, 1942.
14. RUBENSTEIN, B. B.: Am. J. Physiol., **119**, 635, 1937; Endocrinology, **22**, 41, 1938.
- RUBENSTEIN, B. B., and LINDLEY, D. B.: Proc. Soc. Exp. Biol. and Med., **35**, 618, 1937.
15. TOMPKINS, P.: J. Am. Med. Assn., **124**, 698, 1944.
16. WILLIAMS, W. W.: Am. J. Obst. and Gynec., **46**, 662, 1943.



## THE DANGER OF CONTINUED ARSENOTHERAPY IN CASES OF ERYTHEMA OF THE NINTH DAY

BY MAJ. WILLIAM LEIFER, M.C., A.U.S.

CHIEF OF DERMATOLOGY AND VENEREAL DISEASE SECTION ASF REGIONAL STATION  
HOSPITAL, FORT BRAGG, N. C.

THE arsenical reaction termed by Milian<sup>3</sup> "erythema of the ninth day" is characterized principally by fever, malaise and a generalized eruption. Milian's concept that the reaction is due to "biotropism," that is an activation of latent "virus" by the drug, has few proponents today. The consensus is that sensitization to arsenic is the cause.

Moore<sup>4</sup> gives the following description: "The reaction occurs from 5—19 days after the first injection (average 7.8 days) and may follow any of the trivalent arsenicals. It is characterized by a polymorphic erythematous, scarlatiniform, or macular skin eruption accompanied by fever (101°—105° F.), sore throat, headache, malaise, diarrhea, stiffness of the neck and evidence of lymphoid hyperplasia. Its average duration is six days."

There appears to be an inadequate understanding, among practitioners, of the significance of this reaction, particularly of the scope of the disturbance created. Fourteen cases are being reported in which the prompt resumption of arsenical treatment was followed by severe parenchymatous injury. Issue may be taken with the inclusion of some of these cases in the category of "erythema of the 9th day," since no eruption was observed.

Table 1 presents pertinent details. All patients were male soldiers, and none had ever received more arsenic than is stated in the table. They were treated by the then routine antisyphilitic schedule of the Army. For present purposes, only the first 5 weeks of this schedule

TABLE 1.—ANALYSIS OF DATA IN 14 CASES

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age	20	24	37	20	37	20	18	18	25	30	23	19	20	22
Stage of disease	SPP	EL	LL	SNP	SNP	EL	EL	SNP	EL	LL	SNP	EL	EL	EL
Doses of mapharsen before appearance of "Milian" reaction	3	3	3	5	4	4	3	5	4	5	3	4	3	4
Days between first mapharsen injection and appearance of "Milian" reaction	7	8	9	9	10	10	7	9	7	11	6	9	9	10
Eruption	0	0	+	0	+	0	0	+	0	0	0	0	0	0
Additional doses of mapharsen after the "Milian" reaction	2	1	2	2	1	1	1	1	1	2	2	1	1	3
Days between first mapharsen injection and detection of parenchymatous injury	14	14	17	24	13	20	11	16	14	21	17	12	14	24
Type of parenchymatous injury	J	J	J	A	J	A	J	A	J	J	J	J	J	J
	N	N	N				J	N	N				N	N

SNP, seronegative primary syphilis; SPP, seropositive primary syphilis; EL, early latent syphilis; LL, late latent syphilis; J, jaundice; A, agranulocytosis; N, nephritis.

need to be detailed. Mapharsen was given twice weekly and bismuth subsalicylate once weekly. The maximal dose of mapharsen, 0.06 gm., was generally employed, although frequently the initial dose was 0.03 gm. or 0.04 gm.

The reaction occurred 6 to 11 days (average 8.6 days) after the first dose of mapharsen. In 6 cases, it appeared after 3 doses of the drug

had been administered, in 5 cases after 4 doses, and in 3 cases after 5 doses.

Table 2 is a compilation of the symptoms and signs observed in the 14 patients. The only symptoms common to all were fever, headache and weakness. Chills or chilly sensations and gastro-intestinal symptoms were frequent. Five patients had well-marked injection of the conjunctivas with photophobia, and 3 had puffiness of the eyelids and the upper part of the face. Two patients were irrational and had rigidity of the neck, so that a diagnosis of meningitis was considered.

TABLE 2.—SYMPTOMS AND SIGNS OBSERVED IN 14 PATIENTS WITH ERYTHEMA OF THE 9TH DAY

Symptom or sign	No. of patients affected
Fever . . . . .	14
Headache . . . . .	14
Weakness . . . . .	14
Nausea . . . . .	11
Chills or chilly sensations . . . . .	7
Vomiting . . . . .	7
Injection of conjunctivas with photophobia . . . . .	5
Abdominal pain . . . . .	3
Edema about eyes and upper part of face . . . . .	3
Injection of pharynx . . . . .	3
Cutaneous eruption . . . . .	3
Substernal oppression . . . . .	2
Irrational . . . . .	2
Stiffness of neck . . . . .	2
Enlarged, tender cervical nodes . . . . .	2
Anorexia . . . . .	2
Sore throat . . . . .	2
Backache . . . . .	1
Neuritis . . . . .	1

Most interesting was the infrequency of a cutaneous eruption. Both white patients had a generalized morbilliform eruption and 1 of the Negro patients, a mulatto, had a faint pink macular eruption. It is my belief that the reaction was of the same nature in all. In the Negro, the deep natural pigmentation may obscure the pallid, rose-colored macular or scarlatiniform eruption, and also the eruption may be so transient that it will have disappeared by the time the patient is examined. It is entirely possible that the eruption is not an essential part of the syndrome.

In every instance, mapharsen was administered shortly after recovery from the initial reaction, sometimes after a rest interval of a week. Usually there was a prompt recurrence of the original symptoms, but the eruption did not reappear. In only 2 cases was the subsequent dose of mapharsen reduced, to 0.03 and 0.04 gm. respectively, while in the remaining 12 cases the full dose of 0.06 gm. was administered. It was after this additional arsenic that the evidences of parenchymatous damage became apparent (Table 1). The serious complications were observed from 11 to 24 days following the first dose of arsenic, when additional drug had been given a relatively short interval (from 3 to 8 days) after the initial febrile episode. They included

hepatitis, agranulocytosis and nephritis, alone or in combination (Table 1).

All patients recovered, some only after a prolonged and severe illness. For 2 patients, it was subsequently recommended that bismuth alone be given for 4 months, and thereafter arsenoxide with extreme caution. The course of these patients is unknown. The remaining 12 patients received intensive treatment with penicillin (either 1.2 or 2.4 million units of penicillin in 7½ days) without reaction. Their therapeutic result cannot be evaluated at this time.

It is noteworthy that 7 of the 14 patients were either in the hospital at the time of the initial reaction or were admitted because of it, and that the reaction was misinterpreted or minimized. In 1 case the diagnosis was German measles, in another it was common cold, and in the remaining 5 it was thought to be a relatively minor reaction to arsenic. One case is reported in some detail:

**CASE 8.** A white male, aged 18 years, was admitted to the hospital with seronegative primary syphilis. He received the following treatment: August 8, 1944, mapharsen 0.04 gm.; August 10, mapharsen 0.06 gm.; August 12, mapharsen 0.06 gm.; August 14, mapharsen 0.06 gm. He was then discharged, since his penile lesion was healed. During this period there had been no intolerance to the arsenical.

On August 17 (9 days after the first injection), he was given mapharsen 0.06 gm., and about 1 hour later he became weak and dizzy, and complained of feverishness, severe frontal headache, generalized aching pains, nausea and vomiting, and substernal oppression. He was readmitted to the hospital.

Examination revealed injection of the conjunctivas and pharynx, palpable and tender submaxillary nodes, a generalized rose-colored macular eruption and temperature of 103.4° F. The spinal fluid was normal. The white blood cells, examined on two occasions, were 7250 and 7650, with 61 and 53% neutrophils respectively. The urine contained 2+ albumin. A diagnosis of German measles (this disease was then endemic) was made. The fever and eruption had disappeared by August 22, and on August 24 the patient was discharged.

On August 24 he was given mapharsen 0.06 gm., and within an hour he developed severe frontal headache, nausea, vomiting and malaise. He was again admitted to the hospital and found to have fever, puffing of the face, injection of the conjunctivas and pharynx, soft tender nodes under both angles of the jaw, and a blood pressure of 90/50. The urine repeatedly contained albumin, casts and red blood cells. The first white blood cell count was 4100 with 44% neutrophils, but within 3 days the count was 4100 with 3% neutrophils, 1% each of eosinophils and basophils, 86% lymphocytes, and 9% monocytes. Subsequently he developed total agranulocytosis, and there appeared gangrenous pyogenic lesions of the forehead and neck. He was treated with pentnucleotide and repeated blood transfusions with little improvement. It was decided to use penicillin in an effort to control the pyodermas, and he was given a total of 2,880,000 units from August 30 to September 8, 1944. He made a prompt and complete recovery, the pyodermas healing rapidly, and the blood returning to normal. It is anticipated that the penicillin will be "curative" of the syphilitic infection.

**Comment.** Fever in the first 2 or 3 weeks of arsenotherapy may be of different origins. After the initial dose of arsenic, it is usually a manifestation of the systemic Herxheimer reaction. This is especially true of primary and secondary syphilis, less so of latent and late syphilis. The Herxheimer reaction (seen also with penicillin) is ascribed

to massive destruction of treponemes in the circulating blood with release of their toxins or proteins. It does not recur after subsequent injections.

Fever after the second or third, or later, injections of arsenic must be regarded as evidence of toxic reaction or intercurrent infection. It is the intent of this paper to indicate that the safest course is to consider any febrile episode (except the Herxheimer reaction), especially in the first 3 weeks of arsenotherapy, a probable manifestation of sensitivity to arsenic. This is particularly true when the entire syndrome of "erythema of the 9th day" is present. However, it appears to apply with equal force to those cases in which no rash is detected. It is in the clinic and the private physician's office, where patients receive ambulatory treatment and cannot be under close surveillance, that greater awareness of this syndrome is needed. Strict attention should be paid to all reactions following the second and subsequent injections of arsenic, and these should not be minimized.

Erythema of the 9th day is transitory, but nevertheless profound in its disturbances, and not to be underestimated. It is generally held that bismuth may be continued but that arsenic must be deferred for a period of 4 to 12 weeks, and then used cautiously. Many patients will then be found tolerant of the drug. Thus, Cañizares and Thomas<sup>1</sup> state that in their series later reactions were chiefly nitritoid or gastrointestinal. They quote Stokes as having reported a case of exfoliative dermatitis developing when arsenicals were continued. In a later paper, Thomas and Cañizares<sup>6</sup> report 2 cases in which the eruption and general symptoms recurred when arsenic was again given.

Cole, Heisel and Stroud<sup>2</sup> describe a "fever-conjunctival injection-facial edema syndrome" which appeared in 24 patients receiving mapharsen three times weekly. In 17 there were fever, chills, photophobia, nausea, vomiting and general malaise. Shortly after the onset of symptoms the patients showed some conjunctival injection and edema of the face. These symptoms came on after the fifth or sixth injection, and from 9 to 12 days after the first injection. One patient developed icterus which lasted 15 days. In another case an attempt to give neoarsphenamine 12 days after the initial reaction reproduced the reaction along with profound muscular weakness. Three months after the original reaction this patient tolerated 0.01 gm. of mapharsen well. No mention is made of any eruption, and the race of the patients is not stated. This reaction parallels in most respects those described in this paper.

Peters<sup>5</sup> reviewed 54 cases of "erythema of the 9th day," in 2 of which (both Negroes) no eruption was present. Eighteen other colored patients and 34 white patients had a rash. Peters describes the occurrence of visceral reactions along with the initial reaction, before the administration of additional arsenic. These were jaundice in 7 patients, hepatomegaly without jaundice in 4, nephritis in 2, splenomegaly in 1, and granulocytopenia in 1. Of the 36 patients who received further arsenotherapy, 70% had reactions; "53% had serious delayed complications which consisted of dermatitis with and

without exfoliation, jaundice, intolerance to several trivalent arsenical drugs, fever, nitritoid reactions, and recurrent erythema of the 9th day."

It is possible that some of the 14 cases reported here might have shown visceral damage, without additional arsenic. Nevertheless, this arsenic was an added insult, aggravating the already present, but subclinical, parenchymatous injury.

Whether we call this reaction the Milian reaction, "erythema of the 9th day," "early arsenical erythema," or the "fever-conjunctivitis-facial edema syndrome," is of little importance. What is most pressing is that it be recognized as a portentous reaction and regarded with the utmost seriousness. This is particularly vital in view of the ease with which the reaction is minimized or misinterpreted. Serious visceral injury might have been prevented, and certainly would not have been aggravated, if the cases reported had been correctly diagnosed and properly managed.

While it is true that penicillin is rapidly replacing the arsenicals as the therapeutic agent of choice in syphilis, a considerable amount of arsenic will probably be used for some time. The Milian reaction has been observed in diseases other than syphilis, and the arsenicals may continue to be used in non-syphilitic diseases and in certain phases of syphilis.

**Summary.** 1. Fourteen cases of characteristic reaction occurring early in the course of arsenotherapy (6 to 11 days after the first injection) are reported.

2. Only 3 of the 14 patients had a concomitant eruption.

3. The relationship of this reaction to "erythema of the 9th day" is discussed.

4. In all 14 patients early continuation of arsenic after the initial reaction led to serious parenchymatous damage, in the form of jaundice, agranulocytosis, with or without nephritis.

5. The ease with which the reaction is misinterpreted or minimized is indicated, and the need for careful evaluation of fever in the early phases of arsenotherapy is stressed.

6. Twelve of the 14 patients subsequently received an intensive course of penicillin without untoward reaction.

#### REFERENCES

1. CAÑIZARES, O., and THOMAS, E. W.: Early Acute Arsenical Erythemas, A Study of Eleven Cases of the "Erythema of the Ninth Day" of Milian, *Arch. Dermat. and Syph.*, **39**, 867, 1939.
2. COLE, H. N., HEISEL, E. B., and STROUD, G., III.: Intensive Methods of Treating Syphilis, *J. Am. Med. Assn.*, **123**, 253, 1943.
3. MILIAN, G.: Les érythèmes arsenicaux du neuvième jour, *Rev. de méd.*, **37**, 222, 1920.
4. MOORE, J. E.: The Modern Treatment of Syphilis, 2nd ed., Baltimore, Thomas, p. 101, 1941.
5. PETERS, E. E.: The Syndrome of Milian's Erythema of the Ninth Day, *Am. J. Syph., Gonorr. and Ven. Dis.*, **25**, 527, 1941.
6. THOMAS, E. W., and CAÑIZARES, O.: Relapsing Early Acute Arsenical Erythema, Report of Two Cases, *Arch. Dermat. and Syph.*, **42**, 30, 1940.

# POSSIBLE EFFECTIVENESS OF THE L. CASEI FACTOR ("FOLIC ACID") CONCENTRATES ON REFRACTORY ANEMIA AND LEUKOPENIA, WITH PARTICULAR REFERENCE TO LEUKOPENIA FOLLOWING RADIATION THERAPY

BY C. J. WATSON

W. H. SEBRELL

J. L. MCKELVEY

F. S. DAFT

With the technical assistance of MISS VIOLET HAWKINSON

MINNEAPOLIS, MINN.

(From the Departments of Medicine and Obstetrics and Gynecology, University of Minnesota Hospitals, Minneapolis, Minn., and the Division of Physiology, U. S. Public Health Service, National Institute of Health, Bethesda, Md.)

THE effectiveness of the *L. casei* factor and its concentrates in the treatment of leukopenia in rats receiving a deficient diet plus-sulfonamides has been fully established.<sup>1,2,3</sup> These results suggested a clinical trial of *L. casei* factor concentrates in patients exhibiting leukopenia of various cause. In some of these rat studies by Sebrell and his co-workers, not only leukopenia but also an anemia was noted. It was, therefore, determined to employ the material in patients suffering from refractory or aplastic anemia as well as in those in which leukopenia alone of various cause was exhibited. Since 20 micrograms of *L. casei* factor daily for 4 days was quite adequate to correct either leukopenia or anemia, or both, to normal in the rat,<sup>3</sup> an arbitrary dosage of 5 mg. per day for a period of 6 days was decided upon for the human studies. The concentrates available to us contained, respectively, 5 mg. in 7 cc., and 5 mg. in 10 cc.\* It was found that this amount was taken without difficulty and well tolerated given in  $\frac{1}{2}$  glass of milk or tomato juice. In most instances tomato juice was employed. Half of the material was given in the forenoon and half in the late afternoon, in each instance. A total of 17 cases have been studied in this way. The distribution of these cases in terms of clinical diagnosis was as follows:

1. N. W., ♂, 31 (U.H. 739751). Refractory anemia; insecticide exposure.
2. H. G., ♂, 68 (U.H. 740034). Refractory anemia; insecticide exposure.
3. C. E., ♂, 70 (U.H. 740368). Refractory anemia; insecticide exposure.

\* These concentrates of the particular *L. casei* factor described by Hutchings, Stokstad, Bohonos and Slobodkin<sup>4</sup> were supplied through the courtesy of E. L. R. Stokstad of Lederle Laboratories, Inc. In addition to microbiologic potency, the biologic activity of these concentrates was determined. Rats which became leukopenic and granulocytopenic on a purified diet containing succinyl sulfathiazole, were treated with 20  $\mu$ g. per day of *L. casei* factor for 4 days. This was sufficient to bring the leukocyte count of such rats from below 4000, with not more than 5 per cent granulocytes, to 10,000 or higher, with more than 20% granulocytes.

4. H. K., ♀, 28 (U.H. 601008). Refractory anemia; dilantin therapy with skin rash and fever 3 years prior to symptoms of anemia.
5. E. P., ♂, 64 (U.H. 743406). Neutropenia; no known causative factors.
6. B. D., ♀, 19 (U.H. 736826). Refractory anemia; no known causative factors.
7. C. A., ♂, 61 (U.H. 739736). Refractory anemia; insecticide exposure.
8. P. J., ♂, 7 (U.H. 744188). Refractory anemia; following pneumonia and sulfonamide therapy.
9. B. W., ♂, 39 (U.H. 746428). Hodgkin's disease; Roentgen ray leukopenia.
10. B. F., ♀, 23 (U.H. 739188). Rheumatic fever; leukopenia following sulfonamide therapy.
11. W. K., ♂, 67. Polycythemia vera; leukopenia following total body radiation.
12. C. H., ♀, 60 (U.H. 747344). Carcinoma of cervix uteri; Roentgen ray leukopenia.
13. D. K., ♀, 43 (U.H. 740434). Carcinoma of cervix uteri; Roentgen ray leukopenia.
14. M. M., ♀, 67 (U.H. 741624). Carcinoma of cervix uteri; Roentgen ray leukopenia.
15. I. D. W., ♀, 29 (U.H. 743377). Carcinoma of cervix uteri; Roentgen ray leukopenia.
16. I. W., ♀, 41 (U.H. 743337). Carcinoma of cervix uteri; Roentgen ray leukopenia.
17. E. B., ♀, 62 (U.H. 739903). Carcinoma of cervix uteri; Roentgen ray leukopenia.

Additional data for the first 10 cases of the above group (1 to 10 inclusive), and for Cases 12 to 17, are given in Table 1 and Figure 1, respectively. The clinical and laboratory data for Case 11\* are given in the following:

CASE 11. W. K., ♂, 67. Polycythemia vera with hyperleukocytosis. Condition first recognized in 1938 at which time the hemoglobin was 137% (Dare) and the red blood cells were 8.49 millions per c.mm. The leukocytes at that time were 15,050 with 87% neutrophils. The spleen and liver were moderately enlarged. Roentgen ray examination of the gastro-intestinal tract revealed a duodenal ulcer with crater. Roentgen ray therapy totaling 900 r was administered over two gastric portals (in 1938). Blood-letting was performed frequently. During the last 2 years the hemoglobin had decreased so that a hypochromic microcytic type of polycythemia resulted. The leukocytes had steadily risen during this period to a range of 80,000 to 100,000, with 85 to 88% neutrophils, but no evidence of leukemia in the peripheral blood or sternal bone marrow had appeared. Further data in this case are given in Table 2.

**Results.** The results in the first 10 cases, comprising the refractory anemia and toxic leukopenia group, were entirely negative (Table 1).

\* The data from this case were made available to us through the courtesy of Dr. Leon Jacobson, Department of Medicine, University of Chicago.

The only changes observed which might be construed as related to the administration of folic acid were in the group of leukopenias following Roentgen ray therapy (Cases 11 to 17, inclusive). The data are shown in Table 2 and Figure 1.

**Discussion.** Insofar as the refractory anemias were concerned, it was scarcely hoped that the *L. casei* factor concentrates would achieve the beneficial effects observed experimentally,<sup>1,2,3</sup> since there was no reason to believe that a dietary factor was operative in the human disease. Nevertheless, the unknown pathogenesis of human refractory anemia,<sup>4</sup> and, as the name implies, the lack of a successful therapeutic agent made the present trial of *L. casei* factor concentrates a mandatory experiment. It is not possible, on the basis of the condition of the bone marrow, to differentiate between human aplastic anemia and the anemia and leukopenia found in rats receiving sulfonamides. Rat marrows may at times present a picture of actual hyperplasia with a preponderance of immature forms;<sup>6</sup> but at other times<sup>1</sup> the picture is one of profound hypoplasia, very similar to the picture in human aplastic anemia. With respect to a possible dietary factor we were particularly interested in Case 8 of the present series, the only one in which there was a definite history of dietary deficiency. There were, however, no collateral evidences of deficiency. Since this case was that of a child in which infection, sulfonamide therapy and poor diet all had to be considered as possible etiologic factors, we were somewhat more hopeful of a beneficial effect following the folic acid concentrate, but as seen in Table 1, no effect was observed.

At the outset it was decided to include the cases of Roentgen ray leukopenia mainly from the standpoint of permitting comparison with a group in which the etiology was better understood, but with even less hope of benefit than in the more heterogeneous group of cases (1 to 10 inclusive). It was surprising, therefore, to observe a rather consistent increase of the leukocytes following the administration of folic acid concentrate in Cases 11 to 17; *i. e.*, those in which leukopenia resulted from Roentgen ray therapy.

The question at once arises as to whether these increases might not have occurred without the folic acid. In certain instances the application of radium increased the difficulty of interpretation. This is especially true in Cases 12 and 13. In Case 12 a definite rise was observed following folic acid, and then, with continued Roentgen ray, the count returned to just below 2000. Folic acid concentrate was resumed but radium was applied just before the second increase of the leukocytes occurred. In Case 13 the radium was implanted in the middle of the period of folic acid administration and prior to any increase in leukocytes. Shortly thereafter a striking increase occurred and since similar increases are at times noted when radium alone has been used, one cannot, of course, ascribe the rise to the folic acid. In Cases 14 and 16, similar marked increases were observed but in each of these an increase had already taken place before the radium was implanted. One of the most impressive features of the study was the elevation of leukocytes following folic acid in spite of continued radia-



TABLE 1—BLOOD CHANGES AFTER FOLIC ACID ADMINISTRATION

Case No.	Age	Sex	Diagnosis	Blood findings before folio acid				Blood findings (days after commencement of folio acid)											
1 (N. W.)	31	♂	Refrac. anemia poss. due to insecticide; duration 6 mos.	Hb. in gm. per 100 cc. WBC per c.mm. Neutrophils, % Lymphocytes, % Blood transfusions in cc.	4.1 1900 31 69	1 4.0 1500 34 66	3 3.8 1500 34 66	6 4.1 1050 28 72 500	8 5.8 1250 31 68 500	12 8.7 2100 12 87 500	19 14.5 2300 87 Dis. unimpr.	27 10.2 1200 88 Dis. unimpr.							
2 (H. G.)	68	♂	Refrac. anemia poss. due to insecticide; duration 5 mos.	Hb. in gm. per 100 cc. WBC per c.mm. Neutrophils, % Lymphocytes, % Blood transfusions in cc.	3.3 2400 37 63	1 3.18 2300 36 64	3 2.78 1650 54 44	5 2.58 2000 48 52	7 2.9 2400 49 50	8 2.74 2250 56 44 500	9 3.2 2750 58 40 500 Dis. unimpr.	12 3.9 1700 62 38 500 Dis. unimpr.							
3 (C. E.)	70	♂	Refrac. anemia poss. due to insecticide; duration at least 9 mos.	Hb. in gm. per 100 cc. WBC per c.mm. Neutrophils, % Lymphocytes, %	11.3 1200 23 77	1 9.7 800 25 72	3 9.7 1300 24 74	5 10.1 1100 54 44	6 9.4 750 54 39	8 9.2 1000 40 56	10 9.1 1500 28 70 Died	11 9.1 950 30 70 Died							
4 (H. K.)	28	♀	Refrac. anemia of unknown etiology (lengthy mebaral-dilantin therapy for epilepsy); duration 1 yr.	Hb. in gm. per 100 cc. WBC per c.mm. Neutrophils, % Lymphocytes, % Blood transfusions in cc.	6.7 1400 14 86	1 6.0 1200 10 90	3 5.7 3100 14 85	5 5.0 2450 19 75	7 4.4 2400 27 71	9 5.0 1200 24 76 500	10 6.0 2500 20 77 500	21 5.9 1500 6 94 Died.							
5 (E. P.)	64	♂	Neutropenia of unknown etiology, poss. atypical leukemia; necropsy inconclusive	Hb. in gm. per 100 cc. WBC per c.mm. Neutrophils, % Lymphocytes, % Reticulocytes, %	12.0 1100 34 66 0	1 1350 32 68	3 2000 29 71 0.2	5 1950 26 70	7 1450 16 84 0.2	10 7.3 700 28 72	11 7.7 1250 26 74 0.2	7 7.7 1250 26 74 0.2 Died							

6 (B. D.)	19	♀	Refrac. idiopathic anemia of 2 yrs. duration	Hb. in gm. per 100 cc. WBC per c.mm. Neutrophils, % Lymphocytes, % Reticulocytes, % Platelets per c.mm.	6.7 3650 50 48 3.2 144,000	1 6.5 3200 56 44	2 6.5 2200 51 48 2.8	4 7.0 2250 58 42 3.8	7 7.0 2550 36 64 4.0 134,000	9 7.2 2950 32 66	10 7.5 3050 30 69 3.2 120,000	70 6.0 3700 58 42
7 (C. A.)	61	♂	Refrac. anemia of unknown cause; 1½ yrs. duration	Hb. in gm. per 100 cc. WBC per c.mm. Neutrophils, % Lymphocytes, % Reticulocytes, % Platelets per c.mm.	8.9 4200 62 35 0.8 150,000	1 8.4 5900 56 44 0.7 133,000	2 8.9 4000 56 42 1.2	4 7.7 4000 52 46 1.8	7 8.6 6650 33 64 1.5 144,000	12 7.5 3500	15 8.3	22 8.9
8 (P. J.)	7	♂	Refrac. anemia of unknown cause; 1 yr. duration; purpura marked (platelets 24,000 per c.mm.)	Hb. in gm. per 100 cc. WBC per c.mm. Neutrophils, % Lymphocytes, % Reticulocytes, % Blood transfusions in cc.	7.2 2500 28 72 0.9	1 6.6 1900 20 79 1.2	2 6.5 2400 26 73	4 5.6 2450 42 58 1.1	6 5.6 2550 50 50 1.6	7 4.4 1350 38 62 500	8 7.1 2000 37 63 1.4 Unimpr.	26 7.8 1650 30 62
9 (B. W.)	39	♂	Hodgkin's disease; severe leukopenia following extensive Roentgen ray treatment; marked fever	WBC per c.mm. Neutrophils, % Lymphocytes, %	750 67 29	1 650 69 29	3 1000 68 29	6 950 65 32	7 850 63 35	8 750 62 34	11 950 59 38	32 750
10 (B. F.)	23	♀	Rheum. fever; leukopenia for 2½ yrs. following 14 gm. sulfathiazole in 3 days; also persistent rheum. activity varying in degree	Hb. in gm. per 100 cc. WBC per c.mm. Neutrophils, % Lymphocytes, %	11.3 2000 8 90	2 11.2 1600 10 90	4 11.7 2100 14 85	7 11.0 2400 15 80	9 10.8 2300 15 82	11 11.0 2550 21 79	31 11.3 2550 16 84	68 12.3 2700 45 53

TABLE 2.—LEUKOPENIA IN A CASE OF POLYCYTHEMIA VERA FOLLOWING TOTAL BODY RADIATION (CASE 11)												
Date	Hb. (gm. per 100 cc.)	RBC (mill. per c.mm.)	WBC (per c.mm.)	Neutrophils (%)	Lymph. (%)	Mono. (%)	Eos. (%)	Band forms (%)	Retic. (%)	Platelets (per c.mm.)	Remarks	
5-12	11.8	5.80	70,800	87	4	3	6	..	..	..	Total body radiation—	
5-17	12.1	6.20	65,650	84	7	4	5	..	..	..	(200 kv.) 250 r total,	
5-19	11.6	5.50	102,000	84	6	..	6	4	2.1	1,975,000	in divided doses	
5-23	11.0	5.10	77,800	84	4	1	8	3	1.0	1,929,600		
5-27	11.2	5.16	44,000	77	4	..	5	13	1.2	..		
6-2	11.6	5.44	19,500	83	8	..	4	5	0.7	690,000		
6-7	10.0	5.68	18,300	72	4	..	1	23	0.5	392,700		
6-13	10.5	5.35	5,600	64	13	..	3	20	0.2	53,900		
6-16	10.9	5.76	3,900	61	19	..	5	15	0.3	77,000		
6-23	10.0	4.57	1,400	18	43	2	31	6	0.2	146,300		
6-27	..	..	650	9	57	8	22	4	0.1	170,500		
6-29	11.5	5.14	1,400	8	42	10	8	22	..	121,000		
6-30	..	..	1,550	13	44	4	5	34	0.2	..		
7-1	..	..	1,850	19	40	12	4	25	..	..		
7-2	10.5	4.95	2,600	28	38	7	3	24	..	..		
7-3	..	..	2,050	28	23	27	..	28	0.3	..		
7-4	9.8	4.66	3,100	37	30	23	..	10	..	..		
7-5	10.0	4.85	3,700	36	33	16	2	11	0.5	246,400		
7-7	10.9	4.22	7,050	62	..	11	12	15	0.4	286,000		
7-11	11.0	4.24	6,400	72	13	15	..	..	0.5	247,000		
7-18	..	..	7,500	76	16	5	..	3	1.0	..		

Folic acid

tion, as particularly well exemplified in Cases 12, 16 and 17. It has not been possible to obtain control data on this point since, in the past, radiation has not been continued or resumed in the presence of such relatively severe leukopenia as was noted in these cases. It is the gynecologist's (J. L. McK.) impression, on the basis of past experience, that to have continued Roentgen ray therapy under ordinary circumstances in these cases, would have been inadvisable. In Case 13 it

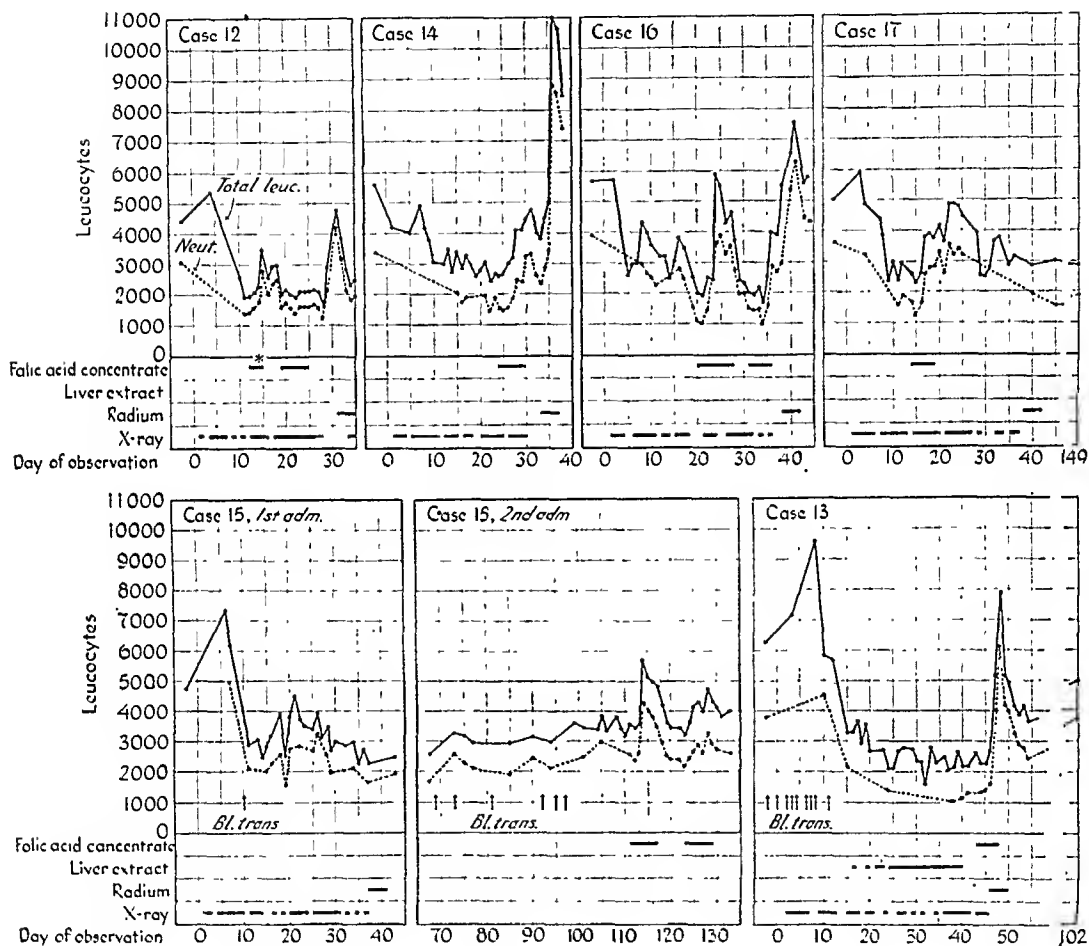


FIG. 1.—Total leukocyte and neutrophil counts in 6 cases of leukopenia following intensive Roentgen ray therapy for carcinoma of the cervix uteri. In each instance a total of 3000 tissue Roentgens was given during the periods indicated. The term folic acid concentrate refers in all instances to the *L. casei* factor (see p. 1).

will be noted that liver extract was given for a considerable period, along with intermittent Roentgen ray therapy, and that during this period the leukopenia was fairly well stabilized. The liver extract used undoubtedly provided small amounts of folic acid although no information is available as to the exact amount. It may be noted that in previous cases, some encouragement was gained when crude liver extracts of this type were used, although only in the sense that the leukocyte count stabilized itself or rose slowly.

One of the most suggestive results in the present group of cases is that seen in Figure 1 (Case 15) in which a mild leukopenia persisted for over 3 months after Roentgen ray therapy for carcinoma of the cervix. The administration of folic acid concentrate in this case was followed on 2 occasions by definite elevations of the leukocyte count. No other stimulating factors were recognized.

We do not wish to draw any conclusions from the results which have just been discussed. It is fully realized that the increase in leukocytes noted in the Roentgen ray leukopenia group has not been proven to be due to the administration of folic acid. At the same time, it is believed that the present results justify further investigation as soon as folic acid becomes available in adequate amounts.

**Summary.** *L. casei* factor ("folic acid") concentrate has been administered orally in 17 cases of refractory anemia or leukopenia. No effect was observed in the 8 cases of refractory anemia, nor in 1 case of leukopenia persisting after sulfonamide therapy. Elevations of the leukocyte count were noted in each of 6 cases with leukopenia resulting from local intensive Roentgen ray therapy for carcinoma of the cervix, and in 1 case of polycythemia vera receiving total body radiation. No effect was observed in 1 case of Hodgkin's disease exhibiting severe leukopenia following intensive Roentgen ray therapy to various parts of the body.

No conclusions may be drawn from the present results. They are communicated at this time for the purpose of stimulating further study of the possible effectiveness of folic acid in the treatment of certain forms of leukopenia, especially that resulting from radiation.

#### REFERENCES

1. SPICER, S. S., DAFT, F. S., SEBRELL, W. H., and ASHBURN, L. L.: Prevention and Treatment of Agranulocytosis and Leukopenia in Rats given Sulfanilylguanidine or Suceinyl Sulfathiazole in Purified Diets, Pub. Health Rep., 57, 1559, 1942.
2. KORNBERG, A., DAFT, F. S., and SEBRELL, W. H.: Production and Treatment of Granulocytopenia and Anemia in Rats Fed Sulfonamides in Purified Diets, Science, 98, 20, 1943.
3. DAFT, F. S., and SEBRELL, W. H.: The Successful Treatment of Granulocytopenia and Leukopenia in Rats With Crystalline Folic Acid, Pub. Health Rep., 58, 1542, 1943.
4. RHOADS, C. P., and BARKER, W. H.: Refractory Anemia, J. Am. Med. Assn., 110, 794, 1938.
5. HUTCHINGS, B. L., STOKSTAD, E. L. R., BOHONOS, N., and SLOBODKIN, N. H.: Isolation of a New Lacto-bacillus Casei Factor, Science, 99, 371, 1944.
6. ENDICOTT, K. M., KORNBERG, A., and DAFT, F. S.: Lesions in Rats Given Sulfathiazole, Sulfadiazine, Sulfanilamide, Sulfamerazine, Sulfapyrazine, or Acetylsulfadiazine in Purified Diets, Pub. Health Rep., 59, 49, 1944.

#### SYNCHRONIZATION OF NEUROTIC BEHAVIOR PATTERNS

By EDMUND BERGLER, M.D.\*

LECTURER AT THE NEW YORK PSYCHOANALYTIC INSTITUTE  
NEW YORK, N. Y.

I. *The neurotic harbors an unconscious "repetition machine."* Every neurotic can be compared to a person carrying around constantly one phonograph record and constantly on the lookout for a phonograph

\* Formerly Assistant Director of the Psychoanalytic Clinic in Vienna.

on which to play his only tune. In this simile the one and only record represents the basic *unconscious* neurotic tendency; the phonograph stands for the other person with whom the neurotic pattern can be repeated. Expressed differently, Freudian psychoanalysis has proven in 50 years of clinical experience that certain unconscious behavior patterns acquired in early childhood become petrified, and under the pressure of the "unconscious repetition compulsion" (Freud) are repeated throughout the remainder of life with eternal monotony—and completely without conscious awareness of that repetition. Thus, the unconscious "repetition machine" reels off the unconscious behavior pattern.

All of this has been known to analysts for many years. The problems which shall be discussed in this paper are:

1. The interrelation of 2 persons repeating respectively corresponding neurotic behavior patterns.

2. The specificity of choice of object for this repetitiveness.

3. The correspondence of "behavior patterns" to specific unconscious defence mechanisms as well as to specific unconscious wishes.

Clinical analysis has proven time and again that chance plays no part in determining the choice of marriage partners. All of the stories promulgated in belles letters to the effect that a normal man becomes the prey of a seriously neurotic woman and, *vice versa*, that a normal woman is taken in by chance and without inner coöperation by a neurotic man, are not based on reality. Such assumptions are necessary in fiction for the furtherance of the plot. Real life is less romantic and more like a textbook of neuroses: *two* neurotics seek and find each other. The neurosis of the husband complements the neurosis of his wife, and *vice versa*. One could call the mechanism involved "unconscious synchronization of neurotic behavior patterns." To apply once more our simile, the marriage partners use each other to reel off their respective unconscious neurotic recordings.

In simple cases this fact is known even to the psychologically-untrained observer. Take, for example, an aggressive woman mistreating her husband, making fun of him in public in a derisive and humiliating way. We have no doubt—other possibilities excluded—that the husband who stands for this sort of behavior must be a weakling of the "milk toast" type. Seemingly, each gets what he wants: she, the pleasure of aggression; he, the pleasure of psychic masochism. Of course, the naive observer will simply say that the poor man had the *misfortune* of picking a shrew. Here the difference in interpretation enters in. The analyst will say that the man unconsciously wanted that "misfortune" and therefore contrived to get it. Furthermore, the words "shrew" and "weakling" or "sissy" are descriptive and not genetic terms. For instance, they do not explain how the aggressive woman happened to become so unpleasant or how the weak man happened to become a "she-" and not a "he-man." The surface description does not even hint at the genetic reasons. The difficulty in explaining this seemingly unreasonable choice increases if, for instance, we find the husband in our example constantly complaining

about his wife's mistreatment and sometimes even rowing violently with her, though he continues to stick to her. How are we to explain the slave-revolt, which obviously corresponds to a "defense mechanism" against his submission?

The decisive question is this: What is repeated and what constitutes genetically these patterns of behavior? Are only unconscious wishes involved or only unconscious defence mechanisms, or both, and if both are involved, what is their respective interrelation?

II. *Six Clinical Examples.* Six patients—3 couples—will be described for the purpose of showing the complicated web of "synchronization of neurotic pattern." All of these 6 patients were analyzed, and the material gathered is based on clinical observation. The summaries presented are sketchy of necessity, for the sake of brevity. For our purpose, *one* segment suffices.

COUPLE A. Mr. A. consulted me because of marital difficulties. He was a good-looking man of 43, with the charm and cynicism of a gamin. He explained his constant conflicts with his wife very simply: He was a "born bachelor," who did not marry, but was married by, his wife. He had warned her, but she had insisted, "and what can you do against a woman's determination?" Of women in general he spoke disparagingly: they were inferior creatures with no brain except for intrigue. I asked him of what his conflicts with his wife consisted. "Oh, she is terrible; she behaves like a governess, makes constant rows, is hysterical and overhearing." "How long did you know your wife before marrying her?" I wanted to know. "A year or so. But never mind, she changed completely. She told me then that she would give me back my freedom if our marriage didn't work. Well, it hasn't in 3 years, and now she refuses to divorce me." Asked what his wife had to complain about chiefly in him, he admitted that he "made some little mistakes." For instance, love letters from other women and his replies came "accidentally" into his wife's hands. He was, constantly reiterated a "born bachelor," and considered himself justified in having extramarital relations. Now, unfortunately, his wife had "material" against him, and that "complicated the matter."

A conversation with Mrs. A., a smart-looking woman appearing not more than 30 (although she was 40) revealed that she considered her husband "a terrible liar, in every respect unreliable, mercenary, and good-for-nothing." She denied that she had forced him to marry her and pointed out what a good influence she had had on him. She admitted that they fought, but shifted the responsibility completely to him. "I never made scenes before I discovered those letters, but afterward I wanted to know the truth." According to her, she quarreled only when her husband came out with "dirty lies." "If he would only confess I would forgive him, but he lies like hell." Asked why she insisted on having all of the details, she answered that she was afraid to meet people any longer, since she didn't know which were his girl friends and which knew about them, and was afraid of becoming a laughing stock. Full of fury, she accused her husband of being a "block of ice." "Of course he has the advantage, since when I react emotionally he calls me hysterical."

From the life story of Mr. A. one could gather that his beautiful mother had had the greatest influence on him, his father having been away often during his formative years. The patient emphasized the beauty of his mother, and it was evident that in his pseudo-charm he identified with her. Very soon it became apparent that he had unconsciously a strong feminine identification. This tendency he counteracted unconsciously with the pose of a Casanova and with

intellectual diapaagement of women. He gave, incidentally, as one of his reasons for allowing himself to "be married by" his wife his desire to break away from his "polysexual life." Without consistency, he stated on the other hand that he preferred his bachelor life. In any case, it became clear that all of the "bad qualities" he accused his wife of having (especially those of an overbearing governess) were exactly the ones which could fulfill his inner wish of being overwhelmed in a feminine way. Unconsciously there was in that layer a complete reversal for them of the man-wife attitude: He played inwardly the rôle of the woman; she, that of the man.

Interestingly enough, the patient was sexually uninterested in his wife. He attributed his lack of interest to two facts: first, that she was not his "type;" and, second, that her constant rows made sexuality impossible. The man was very potent but wanted to be seduced by his wife. She, however, played coy, and was rather passive in sex. One of the patient's chief objections against his wife was that, in a previous relation, she had actually seduced a man, a deed which she had mentioned to him as a practical joke when their acquaintance was slight. The patient dwelt constantly upon this deed, and more reproaches and more refusal in sex and money resulted. Despite the fact that his wife understood vaguely that her husband wanted to be seduced, she felt an inexplicable inhibition against "going back to the old times."

So far we see that the man wanted unconsciously to be overwhelmed in feminine identification—his wife was aggressive. He wanted, furthermore, constant hysterical rows, since they gave him the feeling of being mistreated—she also gave him that satisfaction. But all of these satisfactions were on the unconscious level. Consciously, he suffered "like a dog," to quote him. His wife provided for him only unconscious pleasures on a characterologic level; their sexual life was highly unsatisfactory. There the inner defence on his part set in. What he really wanted was not genital satisfaction; he had used this satisfaction, in previous relations, to a great degree to establish the alibi of being a "he-man." Basically his being mistreated satisfied his sexual needs in a masochistic way. But his constant complaints against his wife represented his unconscious defence. Even in this defence he smuggled in his old wishes; by refusing pseudo-aggressively sex and money, he provoked more aggression on her part and started once more the vicious circle of being unjustly treated.

The strange part in his unsolved œdipal relation was that his wife did not represent his "type," whereas women he had known in previous relations did. Obviously, this was because in marriage his defence had to go one step further in protecting him against his original wish, since it was easier to identify unconsciously his legitimate wife with his mother than girls of indifferent and transitory affairs. Consequently, the defence had to go one step further—avoidance of his "type." Even in his previous transitory affairs, however, it became obvious that our patient was not the great seducer, as he pretended to be. Quite the contrary; these women had to seduce him. By



means of his constant infidelity he tried in vain to prove to himself that he was, not passive, but aggressive toward women.

It might be asked how it happened that a man who had escaped marriage until he was 40 should finally have succumbed to it. The answer is that his original wariness against marriage represented an unconscious desire to avoid greater neurotic troubles, a form of self-preservation of the ego against greater inner danger. But, as is true of old bachelors when they marry, as they do often in their 40's, his neurosis increased with age, and he eventually bargained for greater trouble—and got it. His increasing craving for neurotic pleasure was also visible in his unconscious concocting of the situation in which his wife found the ineliminable letters. Neurotics at that age want to repeat their neurotic repertoire 100%; innuendoes no longer satisfy them.

A few other facts are pertinent with regard to this patient. It was, of course, not true that his father played as unimportant a rôle in his life as he at first claimed. The patient was terrified of his father, and acquired thus strong castration fears which made it possible for him to shift from the identification with the father who possessed the mother ("positive" œdipus complex) to identification with the mother wanting to be overwhelmed by the father ("negative" œdipus). This feminine identification was repressed under the pressure of strong feeling of guilt. Interestingly, the psychopathic trends (lies, unreliability, etc.) could be traced to another identification, with the sister of his mother, who was the black sheep of the family, having various psychopathic symptoms and signs. His identification with her served different purposes: it satisfied the feminine trend in the patient, and could at the same time be used as an ironic weapon against the reproach of his inner conscience that he had such an identification, the unconscious reasoning being, "I cannot be a woman since all women are as impossible as my aunt." In identifying partially with his aunt, the patient also displayed aggression toward his family, thus once more making a play for his typical defence mechanism—pseudo-aggression.

Mrs. A.'s "rows" became so violent that she had to enter analysis, too. It developed that she had come from a family in which the mother was the predominating force. This woman had not only treated her child with coldness and reserve herself but had persuaded the child's father to do likewise. Whether this treatment was guided by some silly pedagogic idea as rationalization or was the mother's means of unburdening her own dislike of her husband was not clear. In any case, the child acquired a deep masochistic attachment to her mother and at the same time a strong aggression as inner defence. She displayed the latter tendency, living a polygamous life which was deeply offensive to her puritanical mother. Her dynamically-decisive masochistic tendency was expressed in the disappointments in life which she constantly brought about for herself. After many circuitous adventures, she married Mr. A., upon whom she unconsciously repeated the child-mother and mother-child situations. Mr. A. was as cold and detached as her mother, and her rows with him represented a futile attempt to get some reaction—even hatred!—from the pre-œdipal mother, her unconscious formula being, "I can't stand that coldness; even your hatred and anger would be more pleasant!" Consciously, of course, she wanted love; unconsciously she got what she wanted.

On another unconscious layer she was as cold and detached as Mr. A. was on the surface; strong narcissistic and unconsciously homosexual identifications were visible on both sides of the union. His unreliability was, by the way, a caricature of her own behavior "in the old days." This former period of polygamous tendencies she sought to counteract by a "model marriage," unfortunately with inadequate means. Unconsciously she knew only too well what to expect from a person of Mr. A.'s type. Not despite but *because* of her unconscious expectation of trouble did she choose him. For masochistic purposes, too, she confessed to him too much of her past.

Besides repeating the child-mother situation (playing again the unhappy child and forcing her husband into the rôle of her bad, cold mother) she also played the reverse situation, causing him to complain of her governess' characteristics.

As is true of all polygamous women who decide to make a break and become "respectable society," Mrs. A. overdid. Therefore she did not make use of her sexual experience and played virgin. Since Mr. A. wanted to be seduced, a stalemate resulted, in which both partners unconsciously enjoyed masochistically the rôle of "being unjustly treated," until their tendencies were solved in analysis.

COUPLE B. Mrs. B. entered analysis because of frigidity. She was married to a man who had lost sexual interest in her a few years after marriage. He claimed, however, that his attitude was the typical one of husbands, pointing out the fact of their 2 children to prove his potency. "In the past," his wife added ironically. He even went to the extent of compiling statistics on the subject, inquiring into the sex life of his friends. Since his friends were no less neurotic than he, his statistics were favorable to his contention. "And that is that," he concluded, and refused ever to discuss the subject further.

However, he had no objections to his wife's analysis, since he regarded her as "highly hysterical." Their marital life centered around one theme: *One of them was always being wronged*. Once the injustice was established, each marriage partner played the following unconscious game: He (or she) did not see that the provocation was his (or her) own. He (she) saw only the injustice, and started, seemingly in self-defence and in righteous indignation, to fight the other bitterly, with the result that both felt deeply hurt and enjoyed unconscious masochistic self-pity. This mechanism, repeatedly described by me<sup>1,2</sup> as the "mechanism of orality" and pathognomonic for a specific type of neurosis (neurosis with oral regression), is characterized by consciousness only of the defensive aggression and self-pity, with repression of awareness of initial provocation and masochistic self-enjoyment. The person suffering from such a neurosis is often considered "aggressive," whereas in reality his surface aggression is but a covering cloak for deep psychic masochism. Genetically, the mechanism has its start in early infancy, arising in the relation to, not the œdipal, but the pre-œdipal mother.

An example of the constant fights of this couple: She forced her husband to spend every Sunday with her mother, though she herself hated her, thus covering her masochistic attachment to her. The poor man had to drive the whole family to the country, miss his rest, swallow his fury, and above all, pretend to be very happy. Driving back once with his wife and mother-in-law in the back seat, he used the brakes too forcefully in stopping, jolting the two women disagreeably. Instantly his wife disparaged his driving ability. Her husband, not knowing that he had unconsciously provoked the scene by his unconscious pseudo-aggression, was helpless, felt unjustly treated, and accused his wife of malicious talkativeness.<sup>3</sup>

Another, less harmless example: By provoking the president of the large concern for which he worked, Mr. B. lost his position, the firm's laconic reason being, "Your personality does not fit into our organization." This was, incidentally, the reason for his wife's forcing him into analysis. He denied

that he had caused his dismissal himself, admitting only to a "perverted sense of humor." In reality, he had antagonized the president at every turn. In reviewing his life history, one could find many other examples of self-damage-ment of the same type.

It is impossible within the bounds of this paper to go into details about this couple, because to do so would necessitate a very technical description of "oral" neurosis in general and oral frigidity in particular, the most complicated of all types of frigidity.<sup>4,8</sup>

It was interesting to observe how the husband reacted to analysis. He regarded it for some time as an academic course, in which intellectual knowledge was to be acquired. His affective understanding was completely lacking. One day he said with disgust, "I see that if I continue analysis you will force me to have sexual relations with my wife, and that is exactly what I don't want." In other words, he wanted to "refuse," knowing inwardly only too well that his refusal provoked once more the masochistic cycle of counter-aggression on his wife's part.

This marriage lasted for 16 years on the basis of "I am unjustly treated," the initial provocation being nicely divided between the two partners.

**COUPLE C.** A 32 year old woman patient had been suffering from agoraphobia for 2 years, and entered analysis because of that symptom. For some months before the start of treatment, she had been unable to work, had given up going to her office, and had sat continually at home, where she felt less fear. To go out alone was impossible for her. She clung to her companion (either her fiancé or her sister, 20 years her senior) as if she were in imminent danger of death. Her fiancé was a gloomy person who looked upon his environment full of suspicion, whose facial expression showed dissatisfaction with everything and everyone. He gave the impression of inner fear, fury, and whimpering at once.

From the curriculum vitae of the patient, who was quite pretty, though colorless and indifferent in appearance, we note: Her father died when she was 10 years old, but she was separated from him in her 7th year, when her parents divorced each other. She described him as an amiable man, though only one episode concerning him remained at first in her memory, that of being taken to his funeral but not crying. Later she recalled other things, which, connected with what her mother had told her of him, gave the following picture: Her father had been industrious and disinclined to drink until about his 50th year (when the patient was 5 or 6); then he underwent a change of character. He suddenly took to drink, became very noisy at home, and started exhibiting himself when drunk. Once in his drunken state he stripped himself naked before the children, and this, after 25 years of married life, served his wife as a signal to leave him, taking the children with her. The man lived 3 years more, took another wife, and saw his children only a few times thereafter. Evidently in order to paralyze his influence, his wife sent the small child to a convent school, to have "good morals" instilled in her. The year in the convent was, according to the patient, the unhappiest of her life. She lived in a constant state of fear, scarcely daring to go to the toilet. The nuns, evidently to prevent masturbation among the children, told them that the devil lurked there. In the course of a few months, the child was turned into a fearful, intimidated personality. By means of desperate pleading she persuaded her mother to take her away from the convent, but thereafter kept up a slight connection with it, attending sewing lessons there.

The patient described the further outward developments of her life as colorless. She was good at her studies and later entered a large concern, where

she had been employed for 12 years at the time of starting analysis. There she was regarded as a person who did not permit herself to be imposed upon and who often came into conflict with her superiors, especially her immediate boss, whom she despised.

The patient could not recall her childhood, and claimed that her first memories were of her 8th year. She denied childhood masturbation, but remembered masturbating in puberty, though she could not recall the fantasies which had accompanied it. When she was 20, she became acquainted with a man considerably older than herself, who suffered from a serious case of tuberculosis and was at times unable to work. She had a sexual relation with this man for 7 years. She described this relation as a very close one, in which she enjoyed complete orgasm. After great conflicts with her mother, an aggressive hypochondriac, who objected to her choice of fiancé because of his illness, she met him outside of her home. Their relationship continued to be good, with great self-sacrifice in nursing him on her part, *until the man was cured of his tuberculosis, when the patient suddenly abandoned him.* According to her rationalization, she realized, as time went on, that her mother had been right in trying to talk her into giving him up because of his illness.

One would expect the patient, having broken off her first engagement because of her fiancé's tuberculous condition, to be more careful in her choice of a second fiancé. By a curious "chance," however, her second betrothed, the man who accompanied her to her analytic appointments and who has been described before, *also suffered from a severe case of tuberculosis.*

The patient's first symptoms of agoraphobia appeared during the last months of her relationship with her first fiancé. She began the second relationship in a period when her symptoms were becoming stronger, and felt, even after the first sexual contact with him, that he was not "the right man" for her. According to her, all tenderness was lacking and he was needlessly and pathologically jealous of her. His jealousy was peculiar: On the one hand he tortured her with accusations of faithlessness; on the other hand he demanded that she be unfaithful to him in the realm of fantasy. He was able to have sexual intercourse only under the following conditions: She must describe to him, *during intercourse*, her intercourse with other men. Since the patient could oblige only with 1 man, her partner had to be contented with stories of imaginary love-affairs. He made her describe in a very realistic manner just how other men conducted themselves during intercourse, what they said, how they reacted, etc. If she refused to do so, the man was impotent or was unable to reach ejaculation during coitus. He demanded further that, in telling the stories, she make use of "popular designations," that is, obscene words. The patient was indignant at her betrothed's requests. Her agoraphobia was setting in more strongly and her sexual desires were diminishing, so that intercourse between the pair became infrequent, and was accompanied by more and more antipathy on her part.

It is impossible to give in this paper the details of the patient's analysis; this has been done elsewhere.<sup>5</sup> Nor is it feasible to enumerate the complicated reasons for this symptom agoraphobia; in the original report 13 determinants are worked out. For our purposes it suffices to state the reasons for the patient's strange choice of fiancé. At the time when her father began to drink, the child was at the peak of her œdipus conflict. During analysis she suddenly remembered that she was the only one who could "tame" him in his drunken state, and that her mother, at a loss to deal with the raving, drunken man, would send her right into his room. This agreed with her mother's report that she was her father's favorite. What took place between father and daughter was at first difficult to reconstruct. There was no proof that the man sexually misused the child. Probably he

exhibited himself and urinated before her. However, we know that for the unconscious, wish and reality have the same psychic value. The fact remains that the child, while in the first critical blossoming of the œdipus complex, found an opportunity to take over the rôle of her mother, indeed, was actually pushed into this rôle by her mother. The patient, however, acquired an exorbitant unconscious sense of guilt, with consequent desire for punishment; for, as may be imagined, her mother's permission went only so far as taking care of the father, not to the extent of realization of the œdipus fantasies. The child unconsciously interpreted her mother's desertion of her father and placing of her in a convent school as punishment. To this was added feeling of guilt because of masturbation.

The conundrum presented by her choice of first fiancé and subsequent leaving of him becomes unraveled if we consider that the patient unconsciously identified him with her father. Her mother's violent effort to make her give up this man was the signal for her neurosis, which had been present since childhood, to become manifest. Her mother's advice mobilized the girl's entire repressed sense of guilt and desire for punishment. In penance she gave up the man, in doing so identifying with her mother, who had given up her husband. The grotesque fact that the patient gave up her first fiancé just as he became cured, only to take up the rôle of nurse to another sick man, can be explained on the basis that for her *illness of the man was a necessary condition for every sexual relationship*, because in her childhood her unconscious œdipus wishes had been permitted only when accompanied by the inner excuse, "I am taking care of my drunken (sick) father." The patient left her first fiancé, *not in spite of but because of his return to health*, when the guilt-relieving fact existed no longer. She then again became attached to a man who fulfilled her inner prerequisite. She stuck to him in spite of her feeling that he was "not the right one" for her and in spite of his repugnant demands *because at this stage in her neurosis he took over the rôle of executor of her desire for punishment*, this extremely neurotic man being well suited to his rôle of jailer.

There were also other factors which contributed to her toleration of her second fiancé. She was herself an exquisite exhibitionist and voyeur, as was visible in her symptom of street-fear. Her main fear, of fainting on the street and thus making a spectacle of herself, especially indicated these traits. Of course, her conflict with her fiancé concerning scopophilia came to the fore under defensive disguise (she apparently objected strongly to his visualizing of sexual scenes between her and other men). On the other hand, the man complained constantly about her own scopophilia. For instance, one morning as they were both going up in the elevator of the building in which they were employed, she opened her coat and noticed that she had "forgotten" to put on a blouse. She reacted to the discovery with hearty laughter, he with an outbreak of rage. On another occasion she injured her knee and displayed her injury quite freely in the office. Occasionally she would fix her eyes on the genital region of men while riding in the streetcar, denying it when her fiancé became enraged.

When the patient's symptoms had subsided considerably and she was approaching cure, her fiancé demanded analysis so urgently that he could not be put off any longer. His conscious reason for entering analysis was his masturbation, which, strangely enough, was accompanied by conscious fantasies of watching his parents have intercourse. His real, unconscious reason for demanding analysis was scopophilia: He believed that something mysterious was going on between his fiancé and the physician, for instance, that she was acquiring some forbidden knowledge which he wanted, too. He simply projected his childhood voyeurism regarding his parents on to his fiancé and the physician. The problem arose as to why in his case the œdipal fantasy of observing the coitus of the parents (he could remember seeing this coitus) had remained conscious and had not been repressed as usual. The answer was that he unconsciously identified with his mother, and as a defence against his feminine wishes, built up his "he-man" attitude. And even this defense was possible only under the disguise that not he but another man had intercourse. Hence his conscious demand that his partner relate her previous sexual experiences. He performed, so to speak, "incognito" or "anonymous" coitus.\* His unconscious reasoning was, "It is not I, but someone else, who does these forbidden things, and since I am neither doing nor saying anything, I cannot be held in any way responsible." So the girl, not he, had to use obscene language. His neurotic jealousy (defence against unconscious homosexuality) also indicated his feminine identification.

The strongest link between the 2 patients was the disguised scopophilia. An additional link was her desire to be mistreated and tormented because of unconscious guilt and his ability to fulfill her desire in his frantic attempt to provide an alibi for his unconscious feminine identification *via* pseudo-aggression. In humiliating the girl by forcing her to use obscene language he worked in the same direction.

**Conclusions.** "Synchronization of neurotic behavior patterns" refers to a married couple's mutual projection of their respective neurotic tendencies upon each other. It is adopted as a compromise of unconscious wishes and defence mechanisms. The contents of the two neuroses thus lived out are by no means simple unconscious wish fulfilments. Quite the contrary, *the stress lies often in the unconscious defence*. The neurotic stability of these relations depends on the segment of projection; the more nearly the two neurotic tangents meet, the stronger the bond. Cases 1 and 2 remained united. The woman of Case 3 gave up her fiancé when his main function—that of executor of her unconscious guilt feeling—had been made superfluous by analysis. In evaluating the stability of such relations, one must also take into account the great tendency toward *narcissistic self-duplication* in the marriage relation. Even partially successful analysis often does not break up such marriages: Narcissism and remnants of the respective neurosis rationalized with external difficulties

\* For details see previous publications.<sup>6,7</sup>

accounts for this fact. Sometimes it is possible to place the old relation on a more normal basis.

The irony in the "synchronization of neurotic behavior patterns" is that the accompanying music is a cacophony of shouts, fights, complaints, reproaches, and tears. Whereas 2 normal persons with similar likes and dislikes achieve some degree of harmony, 2 neurotics with similar "likes" and "dislikes" show on the surface only lack of harmony. The difference is exactly the difference between conscious and unconscious pleasure. The latter, however, must be covered up, and appears only under a palimpsest. Whoever doubts the fact that behind that superficial disharmony lie deep unconscious pleasure and equally satisfying appeasement of the inner conscience in the form of defence mechanisms, should ask himself why these constantly unhappy people, who seemingly hate each other, stick together. Onlookers often venture pessimistic prognoses concerning the future of such marriages. Their prognosis only too often turns out to be erroneous—the glue of neurosis holds such marriages together.

#### REFERENCES

1. BERGLER, E.: *Psychic Impotence in Men*, Monograph Med. Ed., Huber, Berne, p. 72, 1937.
2. BERGLER, E.: *A Clinical Approach to the Psychoanalysis of Writers*, *Psychoanal. Rev.*, 31, 40, 1944.
3. BERGLER, E.: *Logorrhœa*, *Psychiat. Quart.*, 18, 26, 1944.
4. BERGLER, E.: *The Problem of Frigidity*, *Psychiat. Quart.*, 18, 374, 1944.
5. BERGLER, E.: *Psychoanalysis of a Case of Agoraphobia*, *Psychoanal. Rev.*, 22, 392, 1935.
6. BERGLER, E.: *Some Special Varieties of Ejaculatory Disturbances Not Hitherto Described*, *Int. J. Psychoanal. (London)*, 16, 87, 1935.
7. BERGLER, E.: *Obscene Words*, *Psychoanal. Quart.*, 5, 226, 1936.
8. HITSCHMANN, E., and BERGLER, E.: *Frigidity in Women. Nervous and Mental Disease Monographs No. 60*, New York, 1936.

### ATRIAL SEPTAL DEFECT

#### STUDY OF HEMODYNAMICS BY THE TECHNIQUE OF RIGHT HEART CATHETERIZATION\*†

BY EMMETT S. BRANNON, M.D.

H. STEPHEN WEENS, M.D.

AND

JAMES V. WARREN, M.D.

ATLANTA, GA.

(From the Medical and Roentgenological Services of Grady Hospital and the Department of Medicine, Emory University School of Medicine)

ALTHOUGH during recent years the clinical and roentgenologic picture of cardiac septal defects has become more clearly defined,<sup>2,5,12</sup>

\* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Emory University School of Medicine, Atlanta, Ga.

† Part of this material was presented at a meeting of the Mid-Western Section of the American Federation for Clinical Research in Chicago, November 2, 1944.

little knowledge has been gained regarding the altered cardiovascular dynamics in this condition. It is usually stated that blood flows through the atrial septal defect from left to right. If this occurs, the right ventricle must pump not only the normal quota of blood, but in addition that blood which leaks through the septal defect. The evidences of hypertrophy of the right ventricle and the prominence of the pulmonary artery found in patients with atrial septal defect are cited in support of such a belief. The development of the technique of right heart catheterization has allowed us to test this hypothesis and to demonstrate that arterial (oxygenated) blood actually does enter the right atrium in patients with the clinical picture of atrial septal defect. It has also permitted us to exclude the diagnosis of defect in patients with hypertrophy of the right ventricle and prominence of the pulmonary artery due to other causes, by demonstrating that oxygenated blood was not entering the right atrium.

This paper reports observations on 4 patients with the clinical picture of an atrial septal defect in whom oxygenated blood was entering the right atrium.

**Methods.** The method of catheterization of the heart and great vessels utilized in these studies is only slightly modified from that reported by Courmand and his colleagues.<sup>7</sup> The median basilic vein of either arm was exposed through a small incision in the antecubital space. The vein was isolated and a small nick made in its wall. A special radiopaque ureteral type catheter\* (No. 8 or 9) with an angulated tip was then introduced into the vein and passed up the venous channels under fluoroscopic guidance. The catheter was first passed up the arm veins and through the superior vena cava into the right atrium, thence into the inferior vena cava for several centimeters below its entrance into the heart. Throughout the procedure a very slow drip of physiologic saline solution was maintained through the catheter to prevent clotting of blood in its lumen. Before blood samples were drawn for analysis, several cubic centimeters of blood were withdrawn through the catheter and discarded. This avoided any dilution of the sample by the saline contained within the catheter. Samples were then withdrawn, collected under oil, and analyzed for oxygen content by the method of Van Slyke.<sup>10</sup> Only duplicate analyses, which checked within 0.1 volume %, were accepted as satisfactory. After samples were obtained from the inferior vena cava, the catheter tip was withdrawn to the right atrium and finally to the superior vena cava. Specimens for oxygen analysis were obtained from these locations also. In 3 patients the catheter was passed into the right ventricle and in another it apparently passed through the septal defect into the left atrium. Arterial blood for analysis was collected through an inlying needle in the femoral artery, which had previously been well novocainized. The arterial pressure was measured directly by the method of Hamilton<sup>8</sup> and the pressure in the chambers of the heart by either the Hamilton manometer or by a simple saline manometer of the type commonly used for venous pressure measurements. The level of the right atrium was considered to be 5 cm. below the 4th costochondral junction. Oxygen consumption was determined by collecting a sample of expired air in a Douglas bag and analyzing its content by the method of Haldane.<sup>10</sup> From these data the cardiac output was calculated utilizing the Fick principle.

The safety and utility of the methods used in this study have been demonstrated by their extensive use in several laboratories.<sup>7,9,14</sup> In this laboratory over 420 catheterizations have been carried out without any serious untoward effects. Local venous thrombosis at the site of the incision of the vein may

\* Obtained from the U. S. Catheter and Instrument Company, Glenn Falls, N. Y.



occur, but the vein is usually recanalized in 2 to 3 weeks, and several subjects have had multiple catheterizations carried out. Considerable care and gentleness in manipulation are required to obtain satisfactory results. If adequate novocainization is maintained, observation of the type recorded here may be made with the patient quiet and relaxed.

*Observations.* Patients 1 through 4 were subjects who had no evidence of congenital heart disease. Patients 5 through 8 were diagnosed clinically as having an atrial septal defect. Table 1 is a summary of the data obtained in the study of these patients.

The table contains two values for the cardiac index (the cardiac output per sq. meter of body surface). The first is that calculated, as is usually done, utilizing a sample of blood from the right atrium to determine the oxygen content of mixed venous blood. The second value was calculated using the average oxygen content of the blood from the superior and inferior cavæ as the oxygen content of mixed venous blood. In the patients without evidence of congenital heart disease the cardiac indices obtained by the 2 methods agreed very well because the blood in the right atrium was a mixture of that from the superior and inferior cavæ. In the patients with the clinical picture of atrial septal defect the 2 methods gave very different results. The finding that the oxygen content of the atrial blood was higher than that of the blood from the superior and inferior cavæ demonstrated that oxygenated blood, as well as the blood from the cavæ, was entering the right atrium.

The clinical data on Patients 5 through 8 follow:

**PATIENT 5.** A 32 year old colored woman was admitted to Grady Hospital in March, 1944 because of increasing dyspnea of 2 years duration, which had finally reached the stage of orthopnea. Examination on admission to the hospital revealed enlargement of the heart to the left in the 3rd to 5th intercostal spaces, a very loud harsh systolic murmur over the entire precordium, maximal in the 2nd intercostal space just to the left of the sternum. Over this area there was a distinct systolic thrill. There was no diastolic murmur. The pulmonic second sound was markedly accentuated. There was moderate edema of the lower extremities. Roentgen ray examination (Fig. 1) at this time revealed that the heart was markedly enlarged, chiefly to the left (total transverse diameter of the heart 15.9 cm., total transverse diameter of the chest 26.6 cm.). The diaphragms were somewhat elevated. The aortic knob appeared hypoplastic, and the left heart border below the aortic knob bulged outward. Moderate dilatation and striking pulsation of the major branches of the pulmonary artery were noted. The anterior bulging of the heart in the left anterior oblique position was interpreted as enlargement of the right heart chambers. The left atrium was not dilated. An electrocardiogram showed only a tendency toward right axis deviation.

After remaining in bed for several days and receiving digitalis and diuretics, the condition of the patient improved. It was noted that the murmur had diminished considerably in intensity and harshness. At this time the studies summarized in Tables 1 and 2 were performed. In an effort to study the factors influencing the flow of blood through the septal defect, the right atrial pressure was elevated by means of a rapid intravenous infusion of physiologic saline solution. This produced no significant change in arterial oxygen saturation, which might have been expected if the elevated right atrial pressure had caused blood to be shunted from the right side of the heart to the left side. Placing the patient in the left lateral position with the head down and the intravenous injection of 0.16 mg. of epinephrine also failed to produce change in arterial oxygen saturation.

Reexamination of the heart by Roentgen ray at this time (2 weeks after the first examination) showed a decrease in the transverse diameter of the heart (total transverse diameter of the heart 12.7 cm., total transverse diameter of the chest 24.3 cm.). There was no change in the appearance of the pulmonary artery.

On most recent examination (February, 1945) the patient's condition and physical findings were essentially unchanged.

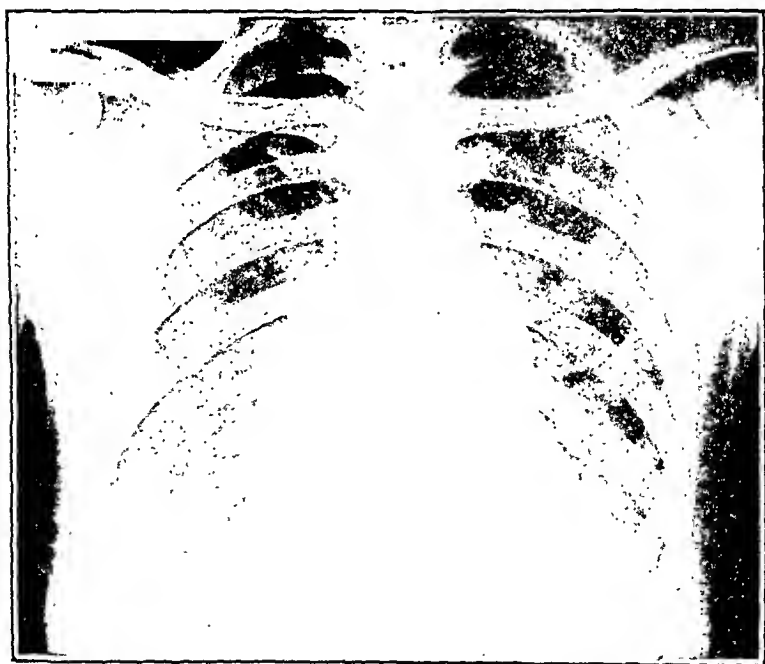
*A**B*

FIG. 1.—Teleroentgenograms of the chest of Patient 5. *A*, On admission to the hospital. *B*, Two weeks later.

The *diagnosis* of an uncomplicated atrial septal defect was made.

**PATIENT 6.** A 68 year old colored female was admitted to Grady Hospital in 1941 because of symptoms related to diabetes mellitus. Although she had no symptoms referable to the cardiovascular system, the heart was enlarged and there was a systolic murmur best heard over the 3rd and 4th left intercostal spaces near the sternal border. The pulmonic sound was accentuated. Roentgen examination revealed that the heart was markedly enlarged in the transverse diameter, chiefly to the left side (total transverse diameter of the heart 15.9 cm., total transverse diameter of the chest 25.6 cm.). The aorta was somewhat elongated and the aortic knob was prominent. The pulmonary artery appeared markedly dilated and showed on fluoroscopy considerable expansile pulsation. There was no enlargement of the left atrium. The right chambers of the heart were found to be enlarged on fluoroscopic examination in the oblique positions.

TABLE 1.—SUMMARY OF OBSERVATIONS ON PATIENTS WITH AND WITHOUT ATRIAL SEPTAL DEFECT

Patient and diagnosis	Oxygen content of blood (vols. %)						Oxygen consumption (cc. per min. per sq. m.)	Cardiac index* (liters per min. per sq. m.)	
	Superior vena cava	Right atrium	Inferior vena cava	Right ventricle	Left atrium	Femoral artery		A	B
1—Bronchogenic carcinoma, hypochromic anemia . . . . .	6.9	6.5	5.9	..	..	10.8	179	4.2	4.2
2—Normal . . . . .	16.5	16.4	17.2	..	..	19.5	123	4.0	4.5
3—Hypertensive vascular disease, cerebral thrombosis . . . . .	14.4	14.2	15.0						
4—Rheumatic heart disease with mitral stenosis, anemina . . . . .	8.2	6.3	6.8	..	..	13.7	165	2.2	2.7
Average—Patients without atrial septal defect . . . . .	11.5	10.9	11.2	..	..	14.7	156	3.5	3.6
5—Atrial septal defect . . . . .	10.4	12.1	9.5	12.8	..	14.1	116	5.8	2.8
6—Atrial septal defect . . . . .	10.1	13.7	12.0	14.1	..	14.8	136	12.4	3.6
7—Atrial septal defect . . . . .	13.4	16.9	13.4	..	18.8	18.7	154	8.5	2.9
Average—Patients with uncomplicated atrial septal defect . . . . .	11.3	14.2	11.6	..	..	15.9	135	8.9	3.1
8—Atrial septal defect with pulmonary vascular disease . . . . .	7.9	12.4	..	12.1	..	13.0	181	30.0	3.5

\* A—Oxygen content of right heart blood used in calculating cardiac output.

\* B—Average content of superior and inferior vena caval blood used in calculating cardiac output.

TABLE 2.—ADDITIONAL HEMODYNAMIC DATA ON PATIENTS WITH ATRIAL SEPTAL DEFECT

Patient	Arterial oxygen saturation (%)	Pressure			
		Right atrial (mm. water)	Right ventricular	Femoral arterial	
				Syst./Diast.	Mean
				Mm. Hg	
5 . . . . .	92	0	40	122/60	81
6 . . . . .	88	60	41	140/60	87
7 . . . . .	91	15	..	116/60	76
8 . . . . .	67	180	112-146	151-166/91	111

Reexamination after 18 days of hospitalization disclosed a striking diminution in the transverse diameter of the heart (total transverse diameter of the heart 12.9 cm., total transverse diameter of the chest 25 cm.). There was no change observed in the appearance of the pulmonary artery or aorta.

The patient was readmitted in April, 1944 for special study. There were still no complaints referable to the cardiovascular system. The physical findings were the same as previously noted. Fluoroscopic and radiographic studies showed no significant change since the previous examination. An electrocardiogram showed right axis deviation. The results of studies at

this time are recorded in Tables 1 and 2. With the patient tilted to the head down position there was no significant change in arterial oxygen saturation.

The *diagnosis* of an uncomplicated atrial septal defect was made.

**PATIENT 7.** A 44 year old white male was admitted to Grady Hospital in March, 1944 for special study of the cardiovascular system. He had experienced dyspnea on exertion for the past 9 years, and occasional attacks of paroxysmal nocturnal dyspnea and orthopnea for the past 3 years.

The heart was found to be enlarged to the left in the 3rd through the 6th intercostal spaces. The rhythm was regular; a low pitched, soft systolic murmur was heard over the 3rd and 4th intercostal spaces. The pulmonic second sound was greater than the aortic second sound. No diastolic murmur was heard. No other abnormalities were detected.

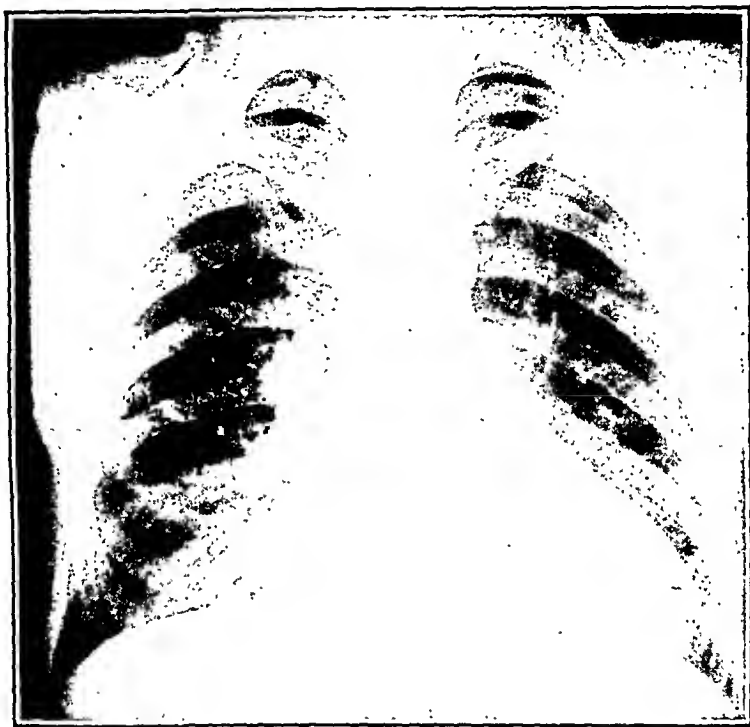


FIG. 2.—Teleoroentgenogram of the chest of Patient 7.

Roentgen examination (Fig. 2) revealed enlargement of the cardiac silhouette toward the left side (total transverse diameter of the heart 15.2 cm., total transverse diameter of the chest 29.8 cm.). The aortic knob was slightly shortened. The major branches of the pulmonary artery revealed only slight accentuation and did not show any unusual pulsation. Fluoroscopically enlargement of both ventricles was demonstrated. There was no enlargement of the left atrium observed. An electrocardiogram showed only right axis deviation.

The results of the special studies on the circulation are recorded in Tables 1 and 2. On 2 occasions the tip of the catheter was advanced so that it first passed to the left from its position in the right atrium, and then headward to form a reversed J shape on fluoroscopic visualization. The pressure at this time was found to be from 0 to 15 mm. of water, using the same reference point as previously, while that in the right atrium was -10 mm. of water. On being tilted in the head down position the arterial blood remained normally saturated with oxygen.

The *diagnosis* of an uncomplicated atrial septal defect was made.

PATIENT 8.\* A 39 year old white male was admitted to Grady Hospital in February, 1945. At the age of 12 he had been told that he had a heart murmur. There was no history of rheumatic fever. At the age of about 26 slight dyspnea on exertion first appeared. This had become progressively more severe and for the past 7 years he had been having occasional attacks of nocturnal dyspnea. One year before admission his physician performed several phlebotomies because of polycythemia.

On admission to the hospital he appeared to be slightly dyspneic while lying quietly in bed. There was moderate cyanosis. The heart was markedly enlarged to the left and right. There was a loud rough systolic murmur over the entire precordium, heard best at the apex and almost completely replacing the first heart sound. At times a low-pitched, rumbling, late diastolic murmur was audible at the apex. The pulmonic second sound was accentuated and was louder than the aortic. The rhythm was regular. There was no clubbing of the extremities.

Roentgenologic examination revealed that the heart was markedly enlarged (total transverse diameter of heart 20.2 cm., total transverse diameter of chest 28.1 cm.). The right ventricle was quite prominent and its pulsations were of increased amplitude. The aortic knob appeared shortened. The pulmonary artery segment of the left heart border was markedly protruding and its pulsations were more prominent than usual. The large intrapulmonary branches of the pulmonary artery were dilated. Some of these branches showed a moderately increased pulsation, whereas others had practically no pulsatory volume changes. The left atrium was questionably enlarged. There was no definite intracardiac calcification demonstrated.

The diaphragms were low in position and showed normal motility. Fibrosis was seen throughout both lower lung fields.

An electrocardiogram showed evidence of marked right axis deviation. Special studies on the circulatory dynamics are summarized in Tables 1 and 2. In addition, the arterial O<sub>2</sub> saturation rose from a control level of 67 to 88% after the patient breathed pure oxygen through a B. L. B. mask for 10 minutes.

The *diagnosis* of atrial septal defect complicated by pulmonary arterial disease and possibly by mitral stenosis (Lutembacher syndrome) was made.

**Discussion.** Detailed studies of the clinical and pathologic picture of atrial septal defect are available.<sup>2,5,12</sup> The patients reported here fit well in all respects. They were all adults, varying from 32 to 71 years in age. One patient denied any symptoms referable to the cardiovascular system (Patient 6). The remaining 3 had noted dyspnea and palpitation on exertion for years and, by the time they were seen in the hospital, had some evidence of congestive heart failure. All 4 patients had physical signs denoting cardiac enlargement. All had a systolic murmur heard along the left border of the sternum from the 2nd to the 5th intercostal spaces. We were impressed by the variation in intensity and quality of this murmur. After prolonged bed rest it was often faint and only moderately harsh, but after even mild exercise it would become much louder and harsher, often accompanied by a thrill. In all patients the pulmonic second sound appeared to be accentuated. Only in 1, Patient 8, was a diastolic murmur audible. This same patient was the only one exhibiting cyanosis, and in this instance there was evidence of complicating pulmonary arterial disease. All patients showed evidence of right axis deviation in their electrocardiographic tracings.

\* This patient was kindly referred to us by Dr. J. C. Mæsse for the special studies reported here.

The roentgenologic findings in Patients 5 and 6 correspond to the classical description of atrial septal defect given by Roesler.<sup>12,13</sup> The characteristic features are marked dilatation and increased pulsation of the pulmonary artery, shortening of the aortic knob and marked enlargement of the right heart chambers. Any of these features may be less pronounced or even absent. Thus in Case 7 the pulmonary artery was only slightly prominent and did not show remarkable pulsation (Fig. 2). On the other hand, one or more of these characteristic roentgenologic signs may be encountered in other forms of heart disease, such as patent ductus arteriosus, cor pulmonale, and rheumatic heart disease. It is for this reason that corroborative clinical and laboratory evidence is necessary for the diagnosis of atrial septal defect.

Roesler<sup>12</sup> differentiating atrial septal defect and patent ductus arteriosus, states that the heart is generally much larger in the former. A similar opinion with regard to cor pulmonale is expressed by Rigler and Hallock,<sup>10</sup> though these authors believe that the distinction between these two conditions depends largely on history and physical signs. It was striking to us that the transverse diameter of the heart in Patients 5 and 6 was markedly and rapidly reduced after treatment of the congestive failure (Fig. 1). Therefore, the characteristic "large" heart was no longer an important feature in differential diagnosis. The concept of the large heart in atrial septal defect is probably based on observations of patients in cardiac failure and on autopsy reports. With newer diagnostic methods it is likely that atrial septal defects may be recognized in patients with little or no cardiac enlargement.

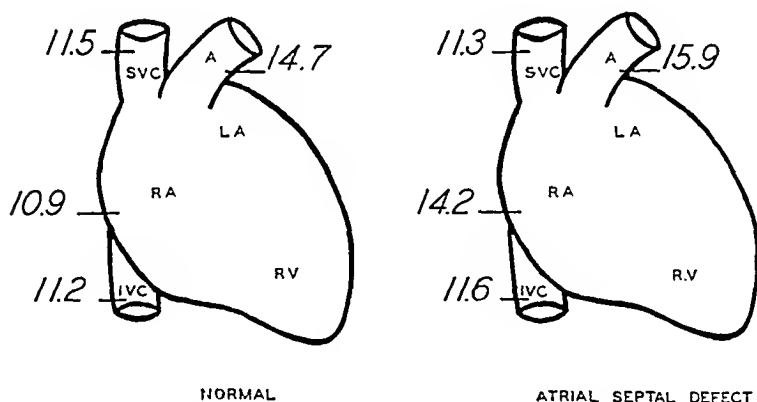


FIG. 3.—Diagram representing a summary of observations on 3 patients with uncomplicated atrial septal defect and 4 patients without evidence of septal defects. The approximate site of obtaining the various specimens is shown by the following: S.V.C., superior vena cava; R.A., right atrium; I.V.C., inferior vena cava; L.A., left atrium; R.V., right ventricle; A., arterial.

In recent years angiocardiology has contributed a great deal to the roentgenologic analysis of cardiac configuration and determination of the size of single heart chambers. The interatrial shunt is, however, only occasionally demonstrated with angiocardiology, and even then with difficulty and not unequivocally.<sup>15</sup> The chief difficulties

are said to be slow injection of the radiopaque material, passage of the injected material into the inferior vena cava, and transient increase in right atrial pressure stopping or reversing the flow through the defect. The latter effect may indeed become helpful in that it will give evidence of the presence of the defect.

The results of the analysis of the oxygen content of vena caval and atrial bloods in Subjects 1, 2, 3 and 4 are essentially what one would expect in a person with a normal heart (Fig. 3). None of these patients had clinical evidence suggesting atrial septal defect. It is to be noted that the average value for the oxygen content of right atrial blood in these patients was 10.9 volumes %, in contrast to 11.5 and 11.2 volumes % for the superior and inferior vena cava respectively. We feel that inadequacy in sampling of the inferior vena caval blood best explains why this value for atrial blood appears to be slightly lower than one would theoretically anticipate. The hepatic veins, which normally carry a rather large amount of quite deoxygenated blood,<sup>17</sup> empty into the inferior vena cava at a point so close to the heart that when the catheter tip is in a position definitely within the inferior cava, it is possibly below the point of drainage of the hepatic veins. As a matter of fact, at times the hepatic veins may empty directly into the right atrium. This position of the catheter below the hepatic veins would fail to take into account the large amount of blood with a low oxygen content coming from the liver. Thus one is not surprised that the actual value obtained on atrial blood may be slightly lower than that from either vena cava. Another potential source of error in sampling of the inferior vena cava is the existence of streams of blood with a high oxygen content coming from the renal circulation.<sup>18</sup>

In Patients 5, 6, 7 and 8 (Fig. 3) there was clinical evidence suggesting the diagnosis of atrial septal defect. The average oxygen content of the right atrial blood obtained from the 3 patients with apparently uncomplicated atrial septal defect was 14.2 volumes % in contrast to values of 11.3 and 11.6 for blood obtained from the superior and inferior vena cava respectively. This demonstrated that oxygenated blood was actually entering the right atrium, presumably passing from the left atrium to the right atrium through the septal defect. The fact that blood obtained from the right ventricle had essentially the same oxygen content as that from the right atrium gave definite proof that there was a real shunt and indicated that the results obtained on atrial blood were not due to passage of the catheter partially through the septal defect. In Patient 7 the tip of the catheter apparently did pass through the septal defect into the left atrium. Blood obtained from this site had the same oxygen content as that of a simultaneously obtained specimen from the femoral artery.

A possible confusing factor in these studies is the uncommon anomaly in which one or more pulmonary veins empty into the right side of the heart rather than into the left side as they normally do.<sup>14</sup> Most frequently such anomalous channels empty into the superior vena cava and would, therefore, be distinguishable from atrial septal defect.

If the rare situation did exist when the pulmonary vein did empty into the right atrium, there would be blood oxygen changes identical to those seen in atrial septal defect.

The cardiac output values are of interest. Since, in the presence of atrial septal defect, much of the output of the right side of the heart returns to the right side of the heart, it is obvious that the output of the 2 ventricles is not equal. If the Fick principle is utilized in the usual way in patients with atrial septal defect, the value obtained is that for the output of the right ventricle. If, on the other hand, a value for oxygen content of mixed venous blood is obtained from the average of the oxygen content of blood from the 2 venæ cavæ, we obtain an approximate value for the output of the left ventricle (Table 1). It may be noted that the values obtained for the output of the left ventricle by such means are in the range of normal subjects obtained by the catheter method.<sup>7</sup> These data give some idea of the functional size of the shunt. In all of our patients the output of the right ventricle was at least twice that of the left. This is an interesting datum when one speculates as to the various factors which control the output of the heart. Although the atrial pressure in the two sides of the heart (*vide infra*) is not greatly different, one is pumping over twice as much blood as the other. A satisfactory explanation for the left right shunt has not been offered.

It is usually stated that the blood flows from the left side of the heart to the right because of the difference in pressure within the two chambers. In Patient 7, where the catheter apparently entered the left atrium, the pressure as measured in the two atria appeared to differ by 10 to 25 mm. of saline. Accurate measurements of this difference are almost impossible because of the velocity of flow from one to the other and changes produced by respiration. Uhley<sup>16</sup> has suggested that the blood flows from the left atrium to the right because of the relative position of the two chambers. He points out that the left atrium is more cephalad than the right with the patient in the upright position. The plane that separates them is horizontal, rather than vertical as is usually supposed. He also notes that most of the difficulty in patients with this type of defect comes in adult life, when the patient is more often in the erect position. We have investigated Uhley's suggestion by attempting to reverse the flow through the defect by standing the patient in the head down position. If the flow from left to right is actually a result of gravity reversing the position of the body should reverse the flow by placing the right atrium above the left. This was tried in 3 patients by supporting them in the head down position. We failed to find any change in arterial oxygen saturation while in this position. If right to left flow had occurred, venous blood would have been shunted into the arterial system, with subsequent diminution in arterial oxygen saturation.

In 3 patients, pressure tracings were obtained from the right ventricle. In 2 instances these were slightly, but probably not significantly, higher than similar tracings obtained in normal subjects in this laboratory<sup>13</sup> and elsewhere.<sup>16</sup> These pressure measurements,



plus those from the right atrium, failed to give any evidence of insufficiency of the tricuspid value. In Patient 8 the systolic pressure in the right ventricle varied between 112 and 146 mm. Hg. In this patient there was also marked arterial oxygen unsaturation, which was relieved to a large extent when the patient breathed pure oxygen. This observation indicated that there was difficulty in oxygenating blood in the lung, rather than an intracardiac shunt, as the cause of the arterial unsaturation. It has been noted previously that atrial septal defect may be complicated by sclerotic changes and thrombosis of the pulmonary vessels.<sup>2,5</sup> It was felt that probably Patient 8 had such changes in his pulmonary vessels.

The elevated right ventricular pressure may, however, be due to other factors. In patients with emphysema and pulmonary fibrosis the right ventricular pressure has been found to be elevated.<sup>13,16</sup> It has also been noted that in patients with mitral stenosis the right ventricular pressure may be abnormally high.<sup>13,16</sup>

Having demonstrated that a left right shunt occurred in patients with the usual clinical picture of atrial septal defect, we have utilized the catheter technique to exclude the possibility of this lesion in patients with hypertrophy of the right ventricle and prominence of the pulmonary artery due to other causes, such as cor pulmonale or pulmonic stenosis.

It would be of interest to apply this method of study in patients with ventricular septal defect. In patients with an atrial septal defect the right ventricular and right atrial blood have essentially the same oxygen content. In the presence of a ventricular defect one would expect that the right ventricular blood would have a higher oxygen content than the right atrial blood because of admixture with oxygenated blood from the left ventricle.

**Summary and Conclusions.** Four patients with clinical evidence suggesting the diagnosis of atrial septal defect have been studied, utilizing the technique of right heart catheterization. The clinical and roentgenologic picture presented by these patients did not differ significantly from that described by others.

The oxygen content of right atrial blood in normal subjects might be expected to be somewhere between the values found for superior and inferior vena cava blood, since blood in the right atrium is a mixture of blood from the venae cavae. This has been verified in 4 normal subjects. On the contrary, right atrial blood from the 4 patients with atrial septal defect had a much higher oxygen content than blood from either the superior or inferior vena cava. This indicated actual shunting of arterial (oxygenated) blood from the left atrium to the right atrium. In 1 patient, the catheter apparently passed through the septal defect into the left atrium and the blood obtained had the same oxygen content as arterial blood.

The right ventricular pressure in 2 patients with uncomplicated atrial septal defect was 40 and 41 mm. Hg. This is probably not significantly above normal. In a 3rd it varied from 112 to 146 mm. Hg. In this patient there was additional evidence suggesting the presence of pulmonary arterial disease.

In all patients with a septal defect the output of the right ventricle appeared to be at least twice that of the left ventricle.

The catheter technique offers a safe and useful method of differentiating atrial septal defect from other causes of hypertrophy of the right ventricle and prominence of the pulmonary artery.

The authors are indebted to Dr. E. A. Stead, Jr., for his advice and help in this work. Miss Eloise Cavin, Miss Maurine Giese, Mrs. Jane Bailey and Miss Lois Jackson gave valuable technical assistance.

#### REFERENCES

1. ABBOTT, M. E.: Atlas of Congenital Cardiac Disease, New York, Am. Heart Assn., 1936.
2. BEDFORD, D. E., PAPP, C., and PARKINSON, J.: Brit. Heart J., 3, 37, 1941.
3. BRANNON, E. S., and WARREN, J. V.: Unpublished observations.
4. BRODY, H.: Arch. Path., 33, 221, 1942.
5. BURRETT, J. B., and WHITE, P. D.: AM. J. MED. SCI., 209, 355, 1945.
6. COURNAND, A., LAUSON, H. D., BLOOMFIELD, R. A., BREED, E. S., and BALDWIN, E. DEF.: Proc. Soc. Exp. Biol. and Med., 55, 34, 1944.
7. COURNAND, A., RILEY, R. L., BREED, W. S., BALDWIN, E. DEF., and RICHARDS, D. W., JR.: J. Clin. Invest., 24, 106, 1945.
8. HAMILTON, W. F., BREWER, G., and BROTMAN, L.: Am. J. Physiol., 107, 427, 1934.
9. McMICAL, J., and SHARPEY-SHAFER, E. P.: Brit. Heart J., 6, 33, 1944.
10. PETERS, J. P., and VAN SLYKE, D. D.: Quantitative Clinical Chemistry, Vol. II. Methods, Baltimore, Williams & Wilkins, 1932.
11. RIGLER, L. G., and HALLOCK, P.: Am. J. Roentgenol., 50, 453, 1943.
12. ROESLER, H.: Arch. Int. Med., 54, 339, 1934.
13. ROESLER, H.: Clinical Roentgenology of the Cardiovascular System, 2nd ed., Springfield, Ill., Thomas, 1943.
14. STEAD, E. A., JR., WARREN, J. V., MERRILL, A. J., and BRANNON, E. S.: J. Clin. Invest. (in press).
15. STEINBERG, M. F., GRISHMAN, A., and SUSSMAN, M. L.: Am. J. Roentgenol., 49, 766, 1943.
16. UHLEY, M. H.: Am. Heart J., 24, 315, 1942.
17. WARREN, J. V., and BRANNON, E. S.: Proc. Soc. Exp. Biol. and Med., 55, 144, 1944.
18. WARREN, J. V., BRANNON, E. S., and MERRILL, A. J.: Science, 100, 108, 1944.

### IDIOPATHIC (?) HYPOPROTHROMBINEMIA

#### REPORT OF A CASE

By V. THOMAS AUSTIN, M.D.

DEPARTMENT OF INTERNAL MEDICINE, CARLE HOSPITAL CLINIC  
AND

HENRY QUASTLER, M.D.

DEPARTMENT OF PATHOLOGY, CARLE HOSPITAL CLINIC  
URBANA, ILL.

We have observed a hemorrhagic disease with a fatal outcome which we cannot identify with any recognized pathologic entity. On analysis of the factors usually involved in pathologic bleeding, a severe hypoprothrombinemia was found. The prothrombin values showed phasic fluctuation not correlated with our therapeutic efforts. There was clinical evidence of liver damage at one time, and at autopsy we found granulomas, probably of tuberculous origin. However, we were not able to recognize in the clinical and pathologic findings any of the known mechanisms of prothrombin deficiency. Hence, we have classi-

fied this condition as idiopathic hypoprothrombinemia. Because this case differs in certain essentials from the 4 previously reported cases of idiopathic hypoprothrombinemia, as indeed the reported cases differ among themselves, we are not of the opinion that these 5 cases represent a pathologic entity. Nevertheless we feel that they should be grouped together pending the development of a more adequate knowledge of the prothrombin mechanism.

**Clinical Course.** The patient, a white male, aged 56, was admitted to this hospital, Feb. 1, 1943, because of bleeding from the nasopharynx and into the tissues of the left leg and thigh of 2 weeks duration. The family history was negative, particularly in regard to hemorrhagic diseases. The past history was essentially negative except for unusual bleeding which attended a hemorrhoidectomy on Oct. 31, 1942, and required suturing of bleeding points on the 4th postoperative day. Further history of possible significance was the death of one of the patient's pure bred bull dogs of leptospirosis in October 1942. Shortly after admission to the hospital further ecchymoses appeared over the right anterior chest wall. The physical examination was otherwise negative except for a sallow color and marked periapical dental sepsis with some bleeding from the gums. The hemoglobin measured 37%. The patient was given a transfusion of 500 cc. of whole blood, and started on parenteral liver extract and liver and iron by mouth. His condition improved steadily until February 17, at which time there was a recurrence of bleeding from the nasopharynx and massive hemorrhages into the calves of both legs, followed immediately by hematemesis and gross hematuria. On February 23, the serum appeared definitely icteric. On February 24, he suffered a severe reaction from a transfusion of 500 cc. of whole blood, and on February 26 became deeply jaundiced. The stools were not acholic. The liver enlarged 3 fingers below the costal margin, and the spleen became just palpable. There was diffuse abdominal tenderness interpreted as indicative of retroperitoneal bleeding. However, this might have been a manifestation of the retroperitoneal growth which was discovered at autopsy.

As indicated in Figure 1, these events were accompanied by an extreme drop in the prothrombin and hemoglobin values and a sharp increase in coagulation time and icterus indices. During this crisis, treatment consisted of daily blood transfusions and intravenous glucose and saline. In addition, he was given parenteral Synkamin (4-amino-2-methyl-naphthol hydrochloride), 1 cc. every 4 hours for 10 doses, followed by 1 cc. daily. The blood factors improved, the bleeding stopped, the fever and jaundice subsided, and there was gradual improvement for 1 month.

On April 1, there was a recurrence of bleeding from the gums, vague abdominal pains, nausea and vomiting. After 2 transfusions, symptoms subsided. However, toward the end of the month there was another profound drop in the prothrombin values followed in a few days by another episode of widespread bleeding into the tissues. Blood transfusions were given almost daily thereafter until the patient died on July 19. A remission, with high prothrombin values occurred between May 8 and 18, followed by another peak of prothrombin values (this one, however, reaching only 45), another low, and a peak of 25. As the chart shows, the undulations of prothrombin values became shorter and shallower. The bleeding became virtually continuous despite therapeutic efforts which included parenteral vitamin K, oral klotogen and bile salts, intravenous calcium gluconate, and multiple vitamins.

On June 10, the patient was transferred to Belmont Hospital, Chicago (service of Dr. O. Richter). A sternal puncture was said to reveal normal marrow components. In addition to the above therapeutic measures the patient was given fibrin and fibrinogen orally, ceanothyn (a ceanothus extract), thromboplastin intramuscularly and cobra venom. In spite of these efforts, bleeding could not be controlled, and on July 11 the patient returned to the Clinic. He was emaciated and there were widespread hemorrhages into the

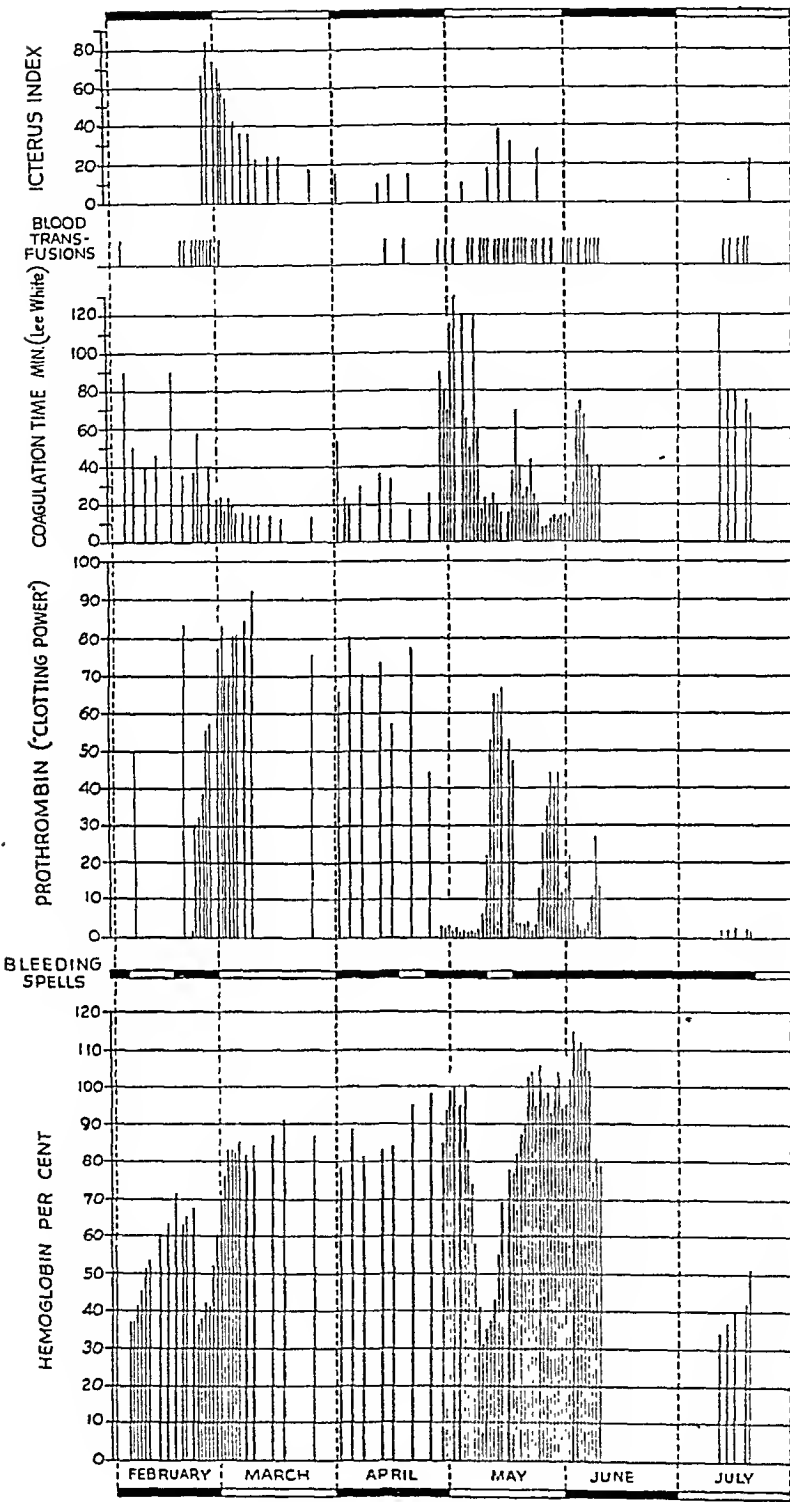


FIG. I

tissues. There had been no further abdominal pains and there had been no enough at any time. On July 18, the signs and symptoms of a cerebral hemorrhage appeared, and on the next day the patient died.

**Laboratory Studies.** The more significant laboratory findings and a few clinical observations are charted in Figure 1. In addition thereto, a roentgenogram of the chest was negative on February 16. The bleeding time (Duke), examined 5 times in February, ranged from 1 min. 15 sec. to 4 min. The platelets, counted 4 times in February, ranged from 198,000 to 277,000. The clot retraction observed on 4 occasions was uniformly very poor. There was no increased fragility of the erythrocytes on February 5. The tourniquet test was negative. The patient belonged to Blood Group III and was Rh-negative. There was no evidence of anti-Rh agglutinins on February 26. The erythrocyte counts roughly paralleled the hemoglobin estimations with color indices of 0.75 to 1. Repeated leukocyte counts ranged from 4850 to 11,850 with no variations in the white cells which could not be accounted for on the basis of blood loss and absorption. The erythrocyte sedimentation rates ranged from normal to 80 mm. in 45 min. An anti-prothrombin assay on February 25 was carried out in the following manner: The patient's blood was mixed with the blood of a normal control in equal parts. The prothrombin time of the control blood was 40 sec. The prothrombin time of the mixture was 60 sec. This limited prolongation was considered due to dilution and was not thought to indicate the existence of an excess of antithrombin or anti-prothrombin in the patient's blood. The seroreactions for syphilis and Weil's disease were negative. The blood calcium measured 9.4 mg. %. On February 26, the total plasma protein was 6.04, the albumin 3.04 and the globulin 2.37 gm. %. The fibrinogen was 0.63 gm. %. The blood urea measured 98 mg. % on February 27, 42 on March 1 and 20 on May 12. A bromsulphalein liver function test on February 22 showed 5% retention of dye in 30 min. and 5% in 1 hour. The Takata-Ara test was done on February 27 and March 2 and showed no precipitation in the first 3 tubes. Urobilinogen was present in the urine and feces on February 27. Urinalyses were not significant except for the episode of gross hematuria and the presence of occasional red cells and casts thereafter.

**Autopsy.** There was evidence of old and recent hemorrhages, widespread throughout the subcutaneous, subpericardial, subendocardial and subperitoneal tissue. There was some fresh blood in the lungs, and in the intestines. The organs showed the changes characteristic of anemia.

The lungs were heavy, their cut surface bluish pink, and the parenchyma of only the right middle lobe was normal. There was a caseous area in the right lower lobe. Three areas of the lungs were examined microscopically. The first section contained several typical tubercles with giant cells in the center, epithelioid cells around them, and a wall of lymphocytes at the periphery (Fig. 2). The second section showed fibrosis, and a few fibrotic tubercles. The third showed frank intraalveolar hemorrhage, and, again, a few miliary foci. No tubercle bacilli were found in appropriately stained slides.

The liver was slightly enlarged, and the interlobar septa more marked than normal. On microscopie examination, the liver cell columns were slightly narrowed. In several areas there were small infiltrates in the center of the acini, some of them consisting of round cells, others chiefly of fibrous tissue (Fig. 3), some were hyalinized. The appearance and distribution of these foci suggested a portal-hematogenous liver tuberculosis of some duration.

Tumor masses were found in large number around the radix mesentery and also along the abdominal aorta, throughout the mediastinum, in the hilum of the spleen, in the parenchyma of the left kidney, all along the greater curvature of the stomach, in several areas of the intestinal wall, and in the tail of the pancreas. The masses could be separated from the spine; they were hard, firm, white and did not show any gross areas of necrosis. Several portions were examined microscopically. One, from the tail of the pancreas showed cells with sparse cytoplasm and large nuclei embedded in a fibrillar stroma. The nuclei were round to oval, contain little chromatin, and several minute



FIG. 2.—Granuloma (tuberculous) in the lung. Giant cells of Langhans type, epithelioid cells, peripheral round cell infiltration. Hem.-eos., 100X.

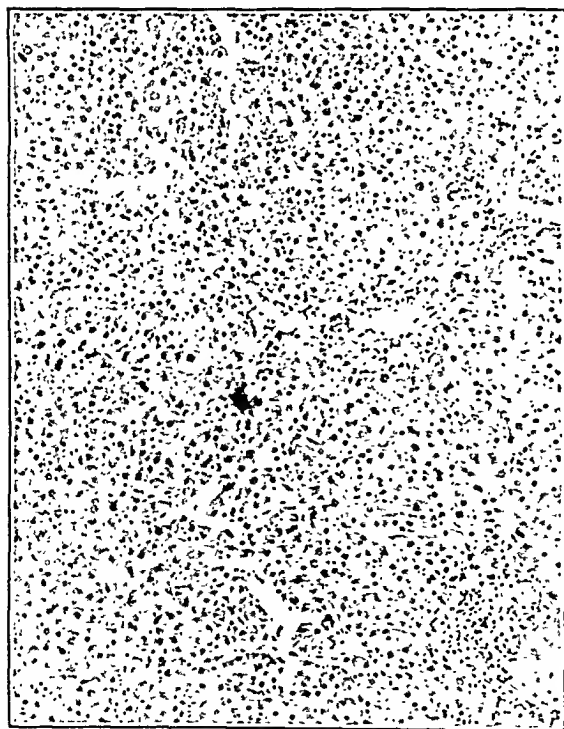


FIG. 3.—Liver. Cell columns slightly narrowed. Fibrous tissue in the lower right corner. Hem.-eos., 100X.

nucleoli. There were giant cells of the Dorothy Reed-Sternberg type: 3 to 6 large, oval, fairly dark, densely packed nuclei. A few eosinophils were lying among the other cells, and there was a fair amount of mitoses present (Fig. 4). Another portion of the tumor showed a few giant cells, but mostly cells of the endothelial type and fibroblasts. There were areas of purely fibrous tissue, some of which were hyalinized. In still another portion, there were chiefly fibroblasts (Fig. 5). A fourth one showed mainly fibroblasts, small cells, and amorphous tissue which did not give the amyloid reaction. No mitoses were seen in this area (Fig. 6). No tubercle bacilli were found on appropriately stained slides of several pieces of tissue. The head was not examined.

**Pathologic Diagnosis.** Hemorrhages and anemia. Granuloma (probably tuberculous) of lungs, liver, lymph nodes. Hodgkin's sarcoma. Possibly sarcoidosis.

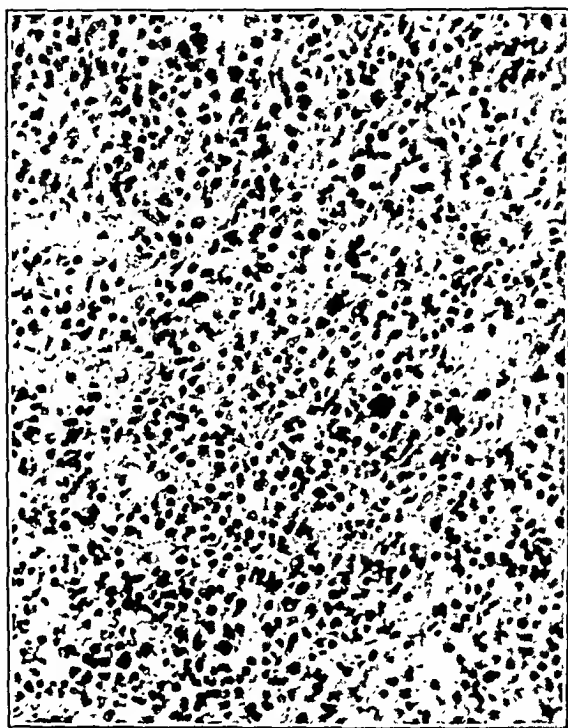


FIG. 4.—Tumor mass in the tail of the pancreas. Giant cells of Dorothy Reed-Sternberg type, and cells of epithelioid character. Hem.-eos., 230 $\times$ .

The pathologic findings, however remarkable, seem inadequate to account for the clinical course of our patient. We may assume that he had a clinically latent tuberculosis of the abdominal lymph nodes, followed in February 1943 by a portal-hematogenous dissemination to the liver, and from there to the lungs. This would account for the episode of hepatic jaundice, as well as for the findings of fibrous tubercles in the liver and lungs. That there was no significant involvement of the lungs prior to this time is evidenced by the negative chest radiogram obtained on February 16. There must have been at least one more dissemination shortly before death as indicated by the presence of acute changes in the lungs. This phase was obscured clinically by the grave complications of repeated hemorrhages.

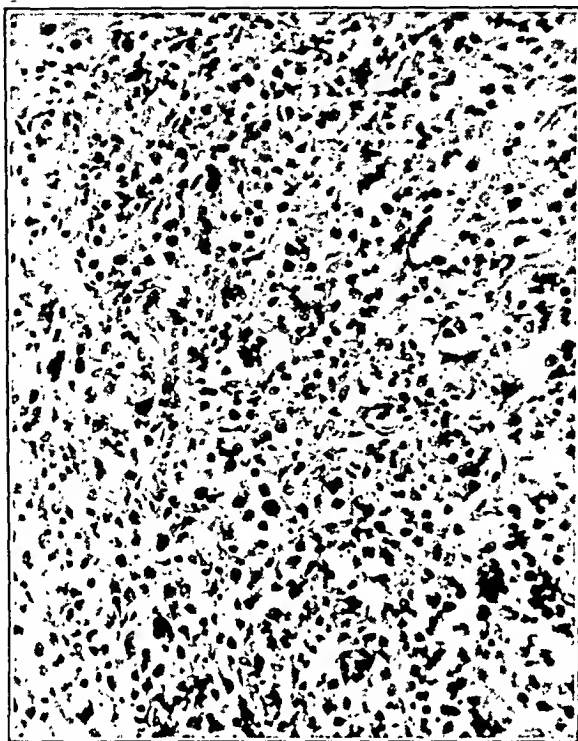


FIG. 5.—Tumorous lymph node. Sparse giant cells, epithelioid cells, and many fibroblasts. Hem.-eos., 230X.



FIG. 6.—Partly hyalinized lymph node. Hem.-eos., 100X.



That tuberculosis and new-growths of sarcoma type may be related is borne out by some references to standard works. Schridde<sup>16</sup> describes a diffuse tuberculosis of the lymph nodes with hyperplasia of endothelioid cells. He finds this condition difficult to distinguish from sarcoma, the differentiation resting on the finding of typical tuberculosis elsewhere in the body, the occasional giant cell and on guinea pig inoculations. Bell<sup>3</sup> notes that "diffuse tuberculosis of the lymph nodes leads to confusion with sarcoma" and further that "difficulties are encountered in differentiating some cases of Hodgkin's disease from sarcoma, largely because the recognized types of malignant lymphomas are not sharply separable." Ewing<sup>5</sup> emphasizes the relationship of lymphosarcoma to Hodgkin's disease, and of both to tuberculosis. He mentions several cases wherein two or all three of these conditions were found in intimate association. He also refers to the rather frequent discovery of tubercle bacilli in lesions supposed to be purely sarcomatous. While recognizing the morphologic entities, Ewing assumes that both Hodgkin's and reticulum cell sarcoma can be caused by tubercle bacilli. The growth tendency, developed under the influence of tuberculo-toxins, can become autonomous and persist independent of the original stimulus. The case here reported belongs to the group of patients with a granuloma (probably tuberculous) associated with endothelial growth. Whether this growth should be called hyperplastic or neoplastic, we do not feel competent to decide. In either case, a causal relationship may be assumed.

We do not, however, recognize a definite connection between the hypoprothrombinemia and the other pathologic conditions. Sheely<sup>17</sup> claimed that the blood prothrombin tends toward lower levels in pulmonary tuberculosis. None of his 106 patients, however, had prothrombin values nearly as low as our patient. Furthermore, Gyntelberg and Dam<sup>7</sup> could not find any significant decrease of prothrombin in tuberculous patients with hemoptysis. Neoplastic diseases, in general, do not decrease the prothrombin values either. Some studies on blood coagulation in neoplastic diseases have been done, but they are isolated and their results controversial.<sup>18</sup>

Hypoprothrombinemia is known to occur in 3 well-defined situations.<sup>4,10,12,14</sup> First, in vitamin K deficiency, either primary or secondary due to faulty absorption from the intestinal tract. Second, in poisoning with dicoumarin and chemically related substances (salicylates<sup>8,11</sup>). Third, in severe liver damage. In addition, 4 cases have been described as "idiopathic hypoprothrombinemia" which do not fit into any of the 3 recognized groups.<sup>2,6,9,15</sup> Here we can exclude vitamin K deficiency as causative factor by the lack of any evidence of malnutrition, and by the therapeutic failure of several vitamin K preparations. We can also dismiss the possibility of drug causation because the patient did not receive salicylates or any other drugs in significant amounts for a significant period of time.

The possibility of liver damage causing the hypoprothrombinemia in our case requires a more detailed discussion. About 1 of 6 patients with hypoprothrombinemia is vitamin K-fast<sup>1,13</sup> and, as a rule, these

cases show severe liver damage: acute yellow atrophy, cirrhosis,<sup>10</sup> metastases,<sup>12</sup> cholangitic cirrhosis, pyelephlebitis with multiple liver abscesses, gas bacillus infection of the liver,<sup>1</sup> and so on. Mild hepatitis is often accompanied by moderate hypoprothrombinemia which responds favorably to therapeutic measures designed to improve the liver function. In animal experiments, only very severe damage to the liver causes significant hypoprothrombinemia; *i. e.*, resection of two-thirds or all of the liver, and long-sustained chloroform anesthesia.<sup>10,14</sup>

There are two significant reasons why we feel our patient's hypoprothrombinemia could not have been due to liver damage. First, the amount of liver damage found at autopsy was small. Second, the timing of the hypoprothrombinemia and the manifestations of liver damage does not bespeak a causal relationship between the two processes. At autopsy, the liver showed some fibrous foci which were interpreted as residual changes of a portal-hematogenous liver tuberculosis. The liver parenchyma as a whole showed very little evidence of damage; not more, in fact, than we are accustomed to seeing in individuals who die after an illness of several months duration. This liver (Fig. 3) does not at all compare with those reproduced by Rhoads<sup>13</sup> where more than one-half of the liver parenchyma was definitely destroyed. It does compare, however, with the liver showing only slightly narrowed cell columns found in a case of idiopathic hypoprothrombinemia.<sup>15</sup>

The patient had 1, possibly 2, severe spells of pathologic bleeding before any liver damage became manifest. The liver function test on February 22, before icterus had developed, gave a negative result. The icterus subsided, but the bleeding spells, with marked delay of prothrombin time, kept recurring. After episodes of bleeding, the patient occasionally became subicteric, without again showing signs of intrahepatic jaundice. Thus, the episode of intrahepatic jaundice, in February and March, began after the bleeding tendency was fully developed, and ended without terminating the hypoprothrombinemia.

After having eliminated the three recognized causes, or groups of causes, of hypoprothrombinemia, *viz.*, vitamin K deficiency, dicoumarin poisoning, and severe liver damage, we compare our case with the 4 other published cases of hypoprothrombinemia of unknown origin. All 5 cases showed severe hypoprothrombinemia with spells of pathologic bleeding, all were vitamin K-fast, none showed any evidence of serious liver impairment, and all had normal platelets. Here, however, the consistency ceases. Important facts of the histories of the 5 cases are tabulated below, and the discrepancies are evident at a glance.

The onset of symptoms occurred in early youth in Cases 1, 2, 3 and 4; in adult age in Case 5. The course was chronic in the former cases; subacute in the latter. The family history was negative in Cases 1, 2 and 5; positive in Cases 3 and 4. The venous coagulation was normal in Cases 3 and 4; delayed in Cases 1, 2 and 5. The clot retraction was not examined in Case 1; it was normal in Case 4, slightly delayed in Case 3, sometimes normal, sometimes poor in Case 2, and always

poor in Case 5. The bleeding time was normal in Cases 1, 3 and 5; sometimes prolonged in Cases 2 and 4. The tourniquet test was not reported in Case 1; it was negative in Cases 2, 4 and 5, and positive in Case 3. Concluding, there are no 2 cases which show identical characteristics in regard to these important factors. It would seem, therefore, that these cases termed "idiopathic hypoprothrombinemia" represent more than one disease. However, we feel that attempts to differentiate should be postponed until more cases are recorded, and more is known about the nature of prothrombin, and the mechanism of its production.

TABLE 1.—CASES OF HYPOPROTHROMBINEMIA OF UNKNOWN ETIOLOGY

Case No.	Author	Age at onset	Family history	Course	Coagulation time	Clot retraction	Bleeding time	Tourniquet test
1	Beard	Infancy	Negative	Chronic	Delayed	Not reported	Normal	Not rep.
2	Rhoads and Fitz-Hugh	Infancy	Negative	Chronic	Delayed	Sometimes normal, sometimes poor	Sometimes normal, sometimes prolonged	Neg.
3	Giordano	5 years	Positive, bisexual	Chronic	Normal	Slightly delayed	Normal	Pos.
4	Murphy and Clark	4 years	Positive, bisexual	Chronic	Normal	Prompt	Frequently prolonged	Neg.
5	Authors	56 years	Negative	Subacute	Delayed	Poor	Normal	Neg.

**Summary.** 1. A case of hypoprothrombinemia has been presented. The disease occurred in an adult male, progressed in spells, and led to death within a few months.

2. Three recognized groups of causes of hypoprothrombinemia, *viz.*, vitamin K deficiency, dicoumarin poisoning, and severe liver damage were ruled out. Hence, the case was classified as "idiopathic hypoprothrombinemia."

3. A comparison of the case here reported with previously reported cases showed certain fundamental differences which would seem to indicate that "idiopathic hypoprothrombinemia" is not a disease entity.

## REFERENCES

- ANDRUS, W. DE W., and LORD, J. W., JR.: *Ann. Surg.*, **112**, 738, 1940.
- BEARD, M. F.: Quoted by Quick.<sup>10</sup>
- BELL, E. T.: *A Text-book of Pathology*, 4th ed., Philadelphia, Lea & Febiger, 1941.
- DAM, H.: *Advances in Enzymol.*, **2**, 285, 1942.
- EWING, J.: *Neoplastic Diseases*, 4th ed., Philadelphia, W. B. Saunders, 1940.
- GIORDANO, A. S.: *Am. J. Clin. Path.*, **13**, 285, 1943.
- GYNTELBERG, E., and DAM, H.: Quoted by Dam.<sup>4</sup>
- LINK, K. P., OVERMAN, R. S., SULLIVAN, W. R., HUEBNER, C. F., and SCHEEL, L. D.: *J. Biol. Chem.*, **47**, 463, 1943.
- MURPHY, F. D., and CLARK, J. K.: *Am. J. Med. Sci.*, **207**, 77, 1944.
- QUICK, A. J.: *The Hemorrhagic Diseases*, Springfield, Thomas, 1942.
- RAPAPORT, S., WING, M., and GUEST, G. M.: *Proc. Soc. Exp. Biol. and Med.*, **53**, 40, 1943.
- RHOADS, J. E.: *Ann. Surg.*, **112**, 568, 1940.
- RHOADS, J. E.: *Internat. Clin.*, **1**, 209, 1940.
- RHOADS, J. E., WARREN, R., and PANZER, L. M.: *Am. J. Med. Sci.*, **202**, 847, 1941.
- RHOADS, J. E., and FITZ-HUGH, T., JR.: *Am. J. Med. Sci.*, **202**, 662, 1941.
- SCHRIDDE, H.: "Lymphknoten," in *Aschoff's Pathologische Anatomie*, II, 7th ed., Jena, Fischer, 1928.
- SHEELY, R. F.: *J. Am. Med. Assn.*, **117**, 1603, 1941.
- STERN, K., and WILLHEIM, R.: *The Biochemistry of Malignant Tumors*, Brooklyn, Reference Press, 1943.

APLASTIC ANEMIA TERMINATED BY REMOVAL OF A  
MEDIASTINAL TUMOR

BY GEORGE H. HUMPHREYS, II, M.D.

AND

HAMILTON SOUTHWORTH, M.D.

NEW YORK, N. Y.

(From the Department of Surgery and the Department of Medicine, Presbyterian Hospital; and the College of Physicians and Surgeons, Columbia University)

TUMORS of the anterior mediastinum may arise from a great variety of structures and their origin is sometimes obscure. Heuer and Andrus<sup>3</sup> have called attention to their diversity and to the fact that many are resistant to radiotherapy, but removable surgically without great difficulty. With the exception of tumors of aberrant parathyroid<sup>1</sup> and those arising from the thymus<sup>5</sup> there are no known mediastinal tumors which have general effects. Tumors apparently associated with anemia, either through influencing blood formation or its destruction, have been reported. Opsahl<sup>7</sup> described a patient with myasthenia gravis who developed aplastic anemia and who at autopsy was found to have a thymic carcinoma; it is not certain, of course, whether this patient's anemia was directly related to the tumor. On the other hand, West-Watson and Young<sup>9</sup> and Singer and Dameshek<sup>8</sup> have each reported a single instance in which a severe anemia was relieved following extirpation of a tumor. In both instances the anemia was of the hemolytic type and the neoplasm was an ovarian teratoma.

Anemia due to hypoplasia of the bone marrow with failure of regeneration of erythrocytes, but no great leukopenia, has been described in infants by Diamond and Blackfan.<sup>2</sup> These children resisted all treatment and could be maintained by repeated transfusions only, but none were associated with any evidence of tumor. Similar types of anemia, also without associated tumor, have been described in adults by Mackey<sup>6</sup> and Kark.<sup>4</sup> In the adult cases, excessive storage of blood pigment in liver and other organs followed prolonged maintenance by blood transfusion and resulted in a terminal picture of hemochromatosis.

The patient whose history is presented here, had a tumor of the anterior mediastinum which appeared to be benign and of epithelial origin. She at no time exhibited any symptoms of myasthenia. Following removal of this tumor the patient's ability to build red blood cells, which had been practically absent for 18 months before operation, returned dramatically to normal. One year after operation the patient developed an apparently trivial infection, after which there appeared ascites, liver enlargement followed by jaundice and death. Autopsy revealed no evidence of the original tumor and an extensive deposit of blood pigment in many viscera suggesting hemochromatosis. This very unusual combination of events warrants publication of a single case in detail.

**Case History.** A 58 year old housewife was admitted to the Presbyterian Hospital for the first time on September 30, 1941, having been sent in by her own physician because of persistent anemia. In 1936 she had pneumonia, which was followed by a mild persistent cough. On October 7, 1938 she first consulted her doctor for a "bronchial cold" with increase of cough, but no fever or hemoptysis. Roentgenogram of the chest showed a large, sharply demarcated, round mass protruding from the mediastinum into the left upper lung field. Between October 29 and November 23, 1938 she was given 1600 R units of radiotherapy. Symptoms of cough subsided and remained absent for 3 months. Cough then reappeared, and between February 4 and March 31, 1939 she received 1100 R units divided equally between anterior and posterior mediastinal fields. No significant change in the size of the mediastinal mass could be demonstrated by roentgenogram.

The patient then felt well until December, 1940 when she developed weakness, fatigability and dyspnea. Her local doctor found her to be extremely anemic (hemoglobin 28%) and admitted her to St. Elizabeth's Hospital, where roentgenograms suggested that the mediastinal shadow had increased somewhat in size. Three transfusions of 500 cc. were given and she was discharged considerably relieved. She then received 8 indirect blood transfusions of 500 cc., on an average of every 3 to 4 weeks. At the same time she took liver extract, thiamin, iron, pentonucleotide and estrogenic hormones with no effect on the anemia.

Examination on admission to the Presbyterian Hospital showed an extremely pale, somewhat obese, middle-aged woman with no evidence of organic disease, other than dullness to percussion with diminished breath sounds over the left parasternal area above the area of cardiac dullness, extending 9 cm. to the left in the 3rd and 4th interspaces. There was a moderately harsh systolic murmur, presumably hemie, at the cardiac apex and transmitted to the base.

*Laboratory examination:* hemoglobin 1.5 gm. (10%); R.B.C. 1,000,000; W.B.C. 10,000 with neutrophils 48 (0-9-39), eosinophils 3, basophils 3, lymphocytes 38, monocytes 8%. Spread: the red cells showed slight anisocytosis but otherwise appeared normal; the white cells were normal adult forms; platelets were plentiful; no parasites were seen; mean red cell diameter 7.2. Blood platelets 204,000. Reticulocytes 0%. Bleeding time 45 seconds. Capillary clotting time  $4\frac{1}{2}$  minutes. Capillary resistance 30. Fragility test normal, hemolysis commencing at 40% saline. Sedimentation rate (Westgren) 60 mm. per 1 hr., but later fell to 28. Urine and stool examinations negative. Wassermann test negative. Serum protein 5.8, albumin 4.4, globulin 1.4. N.P.N. 33 mg. %. Serum cholesterol 101 mg. % with free 30 and esterified 71, but subsequently 155 with free 36 and esterified 119. Serum alkaline phosphatase 3.5 B.U. Serum inorganic phosphorus 3.9 mg. %. Blood group A. Cephalin flocculation negative. Gastric "expression" showed a free acid of 80-20 minutes after histamine injection.

*Roentgenograms* of the skeleton and gastro-intestinal tract, including a barium enema, showed no abnormalities. Films of the chest revealed a well circumscribed, circular shadow projecting from the mediastinum into the left lung field, at the level of the hilum. It was of the same size as in a previous film, and laminographs located it as lying in front of the bronchial tree without deforming it.

*Sternal marrow biopsy* showed mild hypoplasia of bone marrow, but no abnormal cells.

The patient was treated with liver extract (1 cc. of Lederle's Concentrated given intramuscularly daily for 15 days), but had no reticulocyte response. She was given 2 whole blood transfusions and 1 large red cell infusion, and was discharged on October 17, 1941 with a hemoglobin of 51%, R.B.C. 2,400,000. She then took 0.2 gm. of ferrous sulphate 4 i.d. and liver extract was continued. In spite of these measures she was readmitted on November 25, 1941 with a hemoglobin of 20%, R.B.C. 800,000. The blood Kline test on 4 occasions ranged from negative to 4+; the blood Wassermann, however, was

negative in the alcoholic antigen on every occasion. The cholesterol antigen ranged from 2 to 4+. Potassium iodide was given for 9 days as a therapeutic test without any effect upon the mediastinal mass or the persistent anemia. A total dosage of 1500 R of Roentgen ray radiation therapy was then given in 13 exposures. This produced no effect upon the mediastinal mass, which on direct comparison with plates taken 3 years previously appeared to have remained the same size over that period (Figs. 2 and 3). During this admission her blood count was built up by repeated transfusions and red-cell infusions (Fig. 1) to the level of 4,400,000 with 83 % hemoglobin, at the time of discharge on January 7, 1942. On this admission surgical removal of the mediastinal tumor was first considered, but was deferred because of the patient's condition and her reluctance to accept operation. No liver or iron was given because it was felt that a sufficient therapeutic trial had proved them ineffective.

During the next 6 weeks her hemoglobin fell progressively to 26% and 5 transfusions were required to restore it to 75%. Then for 3 months she was maintained by periodic transfusions for each of which she was admitted overnight to the hospital.

She was readmitted to the hospital on June 25 for reconsideration of operation. At that time her hemoglobin was 58% and she appeared pale and weak. She also was suffering from a respiratory infection, accompanied by a moderately severe cough with a temperature of 100.4° F. and some râles at the bases of both lungs. It was felt that when her condition could be sufficiently improved, surgical removal of the mediastinal tumor should be done for 3 reasons: (1) to settle its nature and relationship, if any, to the anemia; (2) because, though stationary in size for 4 years, it might at any time increase in size, in which case it would cause pressure symptoms and be more difficult to remove; (3) any such tumor is capable of malignant degeneration. On conservative treatment her temperature returned rapidly to normal and her respiratory symptoms disappeared within the first week. After receiving 3 transfusions, she refused operation and returned to her home.

During August and September she was admitted periodically for transfusions, but on 3 occasions had reactions (chill, fever and once vomiting and a sense of choking). She began to dread receiving blood and her hemoglobin averaged only about 40% during the period. Palpitation, tachycardia, and ankle edema developed, though her venous pressure after a few hours of bed rest was 90 mm. of saline. By October she had decided to accept operation in the hope that it might help her anemia, though no real expectancy of such an effect was held out to her.

She was readmitted on October 6, 1942. During the next week she received 2500 cc. of whole blood in 3 transfusions with a resultant rise of hemoglobin from 30 to 60%, and of red cells from 1,300,000 to 4,000,000. No reticulocytes were found on 3 counts at different times.

On October 16, 1942 a spherical tumor mass was removed from the anterior mediastinum through a transpleural approach. The tumor was solid and well encapsulated, lying in close approximation to the pericardium inferiorly and posteriorly, and extending up across the pulmonary artery superiorly to the aortic arch. Laterally it was bounded by the mediastinal surface of the left upper lobe to which it was quite adherent. Medially the fatty tissue of the anterior mediastinum was also adherent to it, and from this tissue numerous blood-vessels of moderate size entered the tumor. In order to excise the tumor it was found necessary to divide the left phrenic nerve, after which the mass was shelled out without difficulty. The mediastinal pleura was closed and the chest closed without drainage after reexpansion of the left lung. She was given a transfusion of 1000 cc. of whole blood on the operating table.

*Pathologic examination* of the tumor showed it to be a soft, fleshy, light-colored tumor mass of homogenous structure, measuring 8 x 6 x 5 cm. and weighing 185 gm. (see Fig. 5). Fine lobulations were apparent, but no areas of degeneration or cyst formation.

*Microscopic examination* showed a uniform cellular tumor consisting of 2 cell types (Fig. 6). The most prominent were moderate-sized, spindle-

shaped, well defined cells with plump oval nuclei, arranged in no definite pattern. Cells of the other type were scattered irregularly throughout the tumor; they had small, dark, dense nuclei, and in most respects appeared identical with the many lymphocytes seen in the vascular channels. No

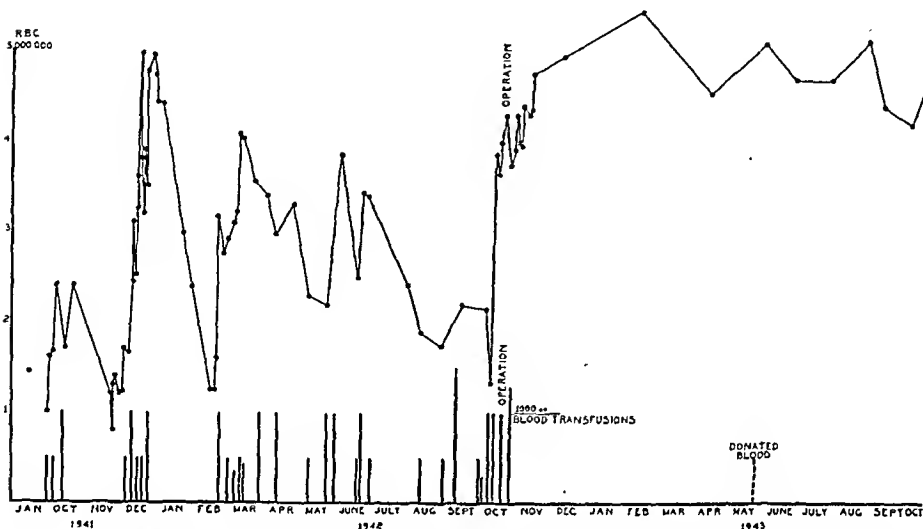


FIG. 1.—Chart of blood cell counts. Note the changes in erythrocyte count in relation to repeated transfusions and operation.



FIG. 2.—Roentgenogram of chest in 1938. There is a large circumscribed circular shadow protruding from the mediastinum into the left lung field.

mitotic figures were seen. The tumor was encapsulated by a relatively acellular and avascular tissue which was not infiltrated by the tumor cells. The origin of the tumor was not apparent. However, it was considered probable that the tumor was not malignant and further study with special stains

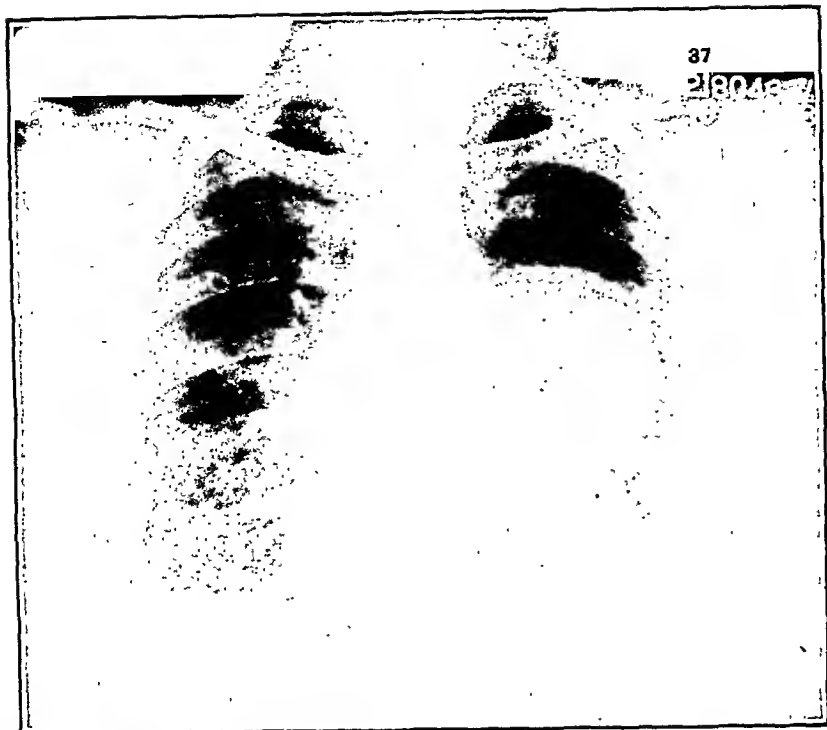


FIG. 3.—Roentgenogram of chest in 1942—a few days before operation. The mediastinal shadow shows practically no change when compared with picture taken in 1938.

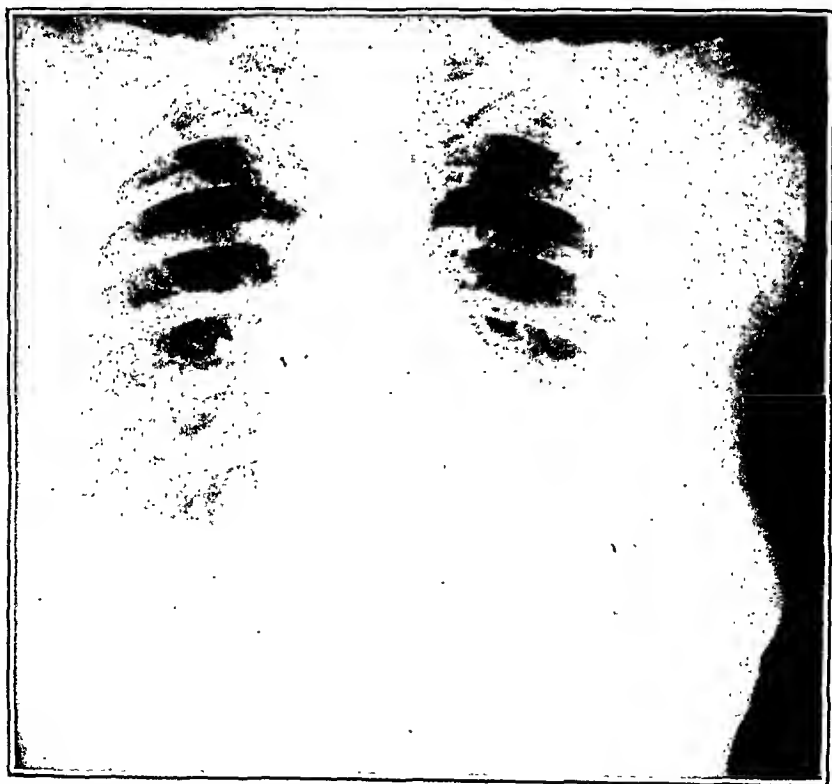
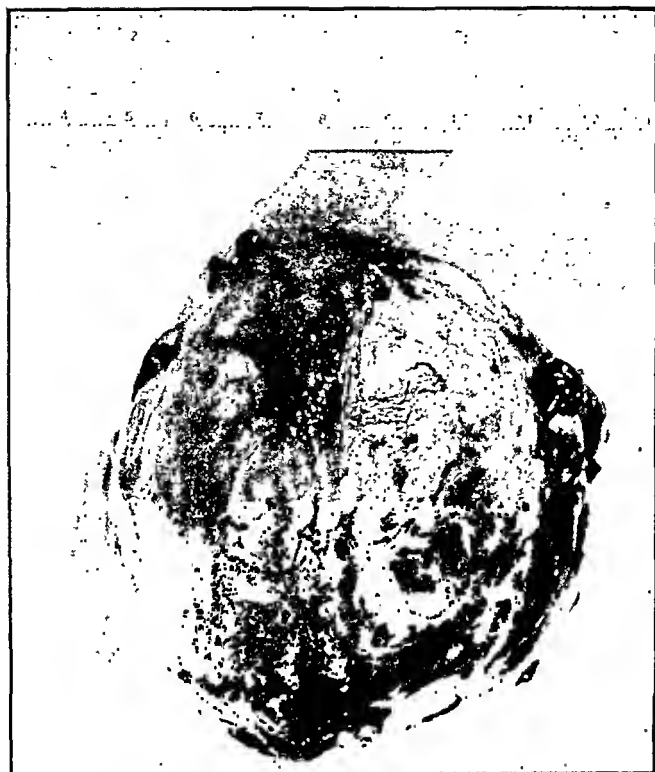
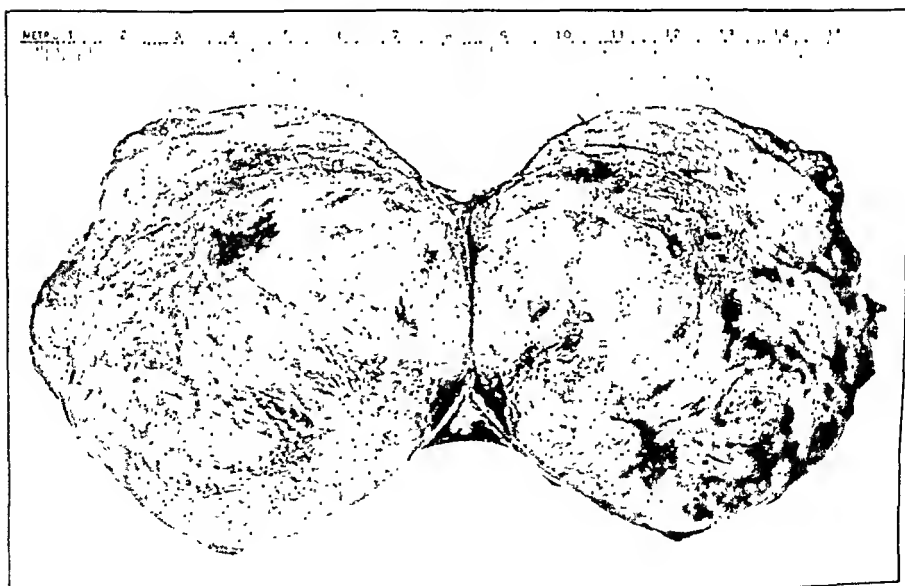


FIG. 4.—Roentgenogram of chest in 1943—10 months after operation. The left diaphragm is high due to the division of the phrenic nerve at operation. There is no evidence of recurrent tumor.





A



B

FIG. 5.—Photograph of tumor. A. External appearance. B, Tumor divided to show gross appearance of interior. There is no obvious lobulation and no degeneration.

revealed certain concentrically layered, solid bodies with flattened cells at their peripheries which suggested degenerated Hassall's corpuscles. Because of these and the uniform presence of the two cell types, one resembling a lymphocyte and the second a reticulum cell, the tumor was thought by Dr. Purdy Stout to be possibly of thymic origin. On the other hand Dr. A. M. Pappenheimer thought that a thymic origin was unlikely, because there was not the intimate mingling of lymphocytes and reticulum cells customarily found in thymic tumors, and because the argyrophil stroma was too abundant and tended to encircle individual cells. Unfortunately, the tumor tissue was fixed before it was appreciated that there was any relationship between the tumor and the anemia. For that reason no chemical or biologic studies were done.

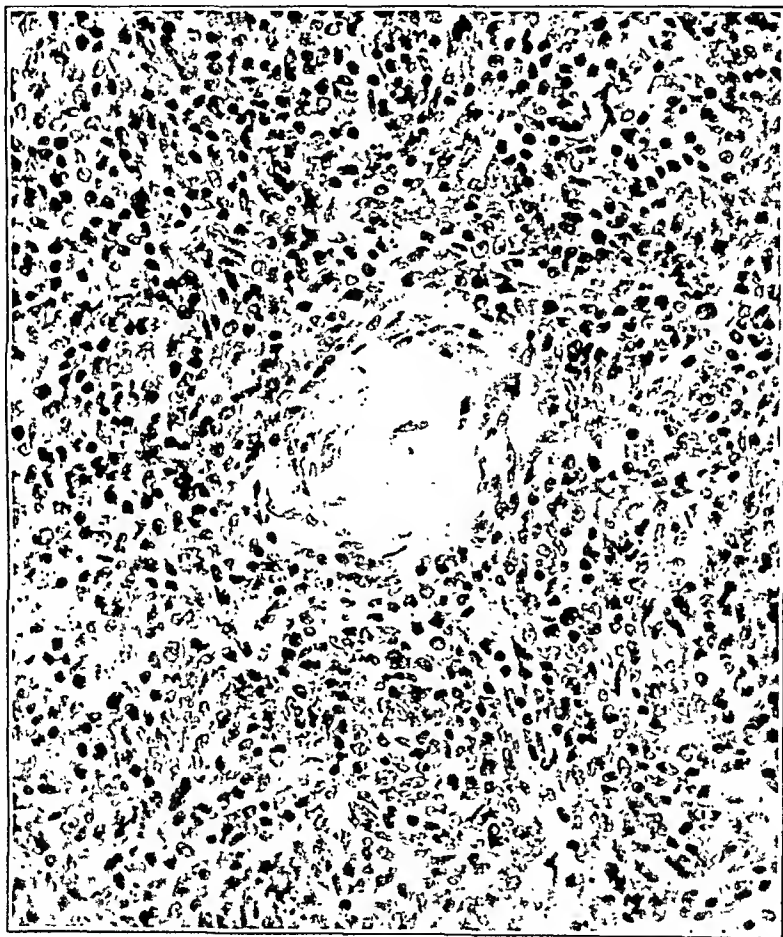


FIG. 6.—Photomicrograph of tumor, showing characteristic histology. The cells are of two types—one resembling a lymphocyte and the other a larger cell. In the center is an island of hyaline tissue, possibly representing a degenerated Hassall's corpuscle.

She reacted well to operation, though the left lung became atelectatic due to paralysis of the diaphragm and the accumulation of a moderate amount of fluid. Her temperature rose to 102° F. on the 2nd day and remained slightly elevated for 10 days, after which it returned to normal. The wound healed primarily and she was allowed up on the 8th day, walking on the 13th. On

the 3rd day after operation reticuloeytes (0.8%) were found for the first time since she had been followed in this hospital. During the next week her red count decreased, but her reticuloeytes increased steadily to a peak of 16.5% on the 20th day after operation. Their level then fell to 7.3% on discharge, 4 weeks after operation, at which time her red count was 4,780,000 (Fig. 7). She received no whole blood after the transfusion on the operating table, but on the 10th postoperative day was given a red cell infusion equivalent to 1300 cc. of whole blood.

During the year following discharge she received no further transfusions. Her hemoglobin varied between 90 and 108%, and her red count between 4,900,000 to 5,450,000. Her general improvement in strength and vigor was dramatic and though her left diaphragm remained markedly elevated, she had no complaints of dyspnea or weakness until September, 1943. In May, 1943 she donated 500 cc. of blood to the hospital. The next day her hemoglobin was 103%, her red count 4,700,000 and she showed a reticuloeyte response of 1.5%.

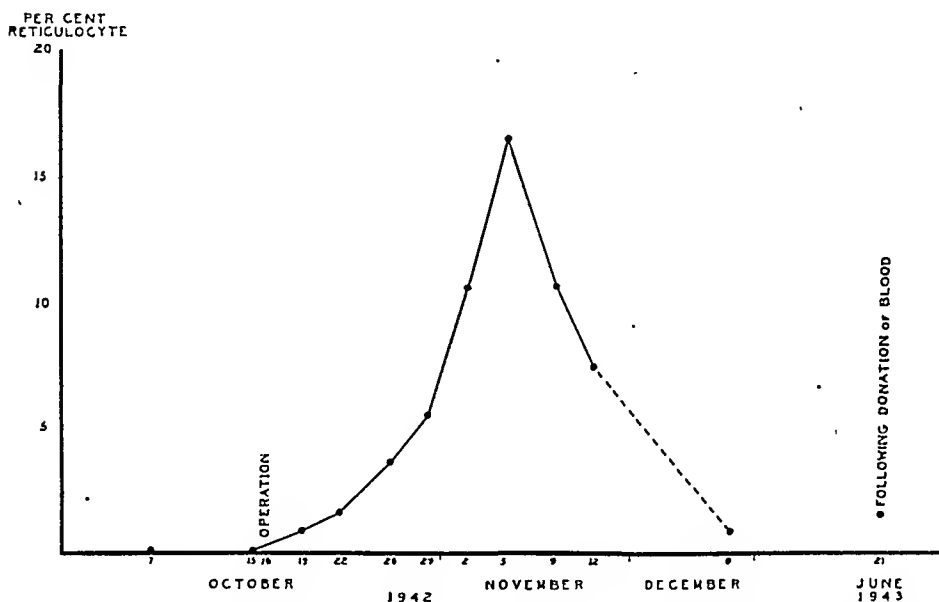


FIG. 7.—Chart of reticulocyte response. A chart to show the reticulocyte response which followed operation. During the rapid rise in the last 2 weeks of October, the erythrocyte count rose to normal, where it remained following the fall in reticulocyte count (see Fig. 1).

In August, 1943 she developed a femoral lymphadenitis, resulting from a secondarily infected epidermophytosis of the left foot, for which she was readmitted to the hospital. Physical examination at this time showed her to be well nourished and not acutely ill. The thoracic scar was well healed and examination of the lungs showed only flatness and absence of breath sounds in the left lower lobe region where Roentgen rays had demonstrated a high diaphragm (Fig. 4). The abdomen was obese, making examination difficult, but there was a sense of resistance in the right upper quadrant suggestive of an enlarged liver. No definite margin could be felt. There was a large area on the medial aspect of the left thigh, just below the inguinal ligament, which was red, indurated and tender but which showed no fluctuation. No abnormal skin pigmentation was present. The urine showed no abnormality. The red

count was 5,100,000; white count 13,100 with 72% polys. Fasting blood sugar was 120 mg. per 100 cc. Temperature, which was 102° F. on admission, fell to normal 12 days later but then rose again and fluctuated between 100° and 103° for the next 5 days during which she received sulfadiazine by mouth. The area of inflammation was then incised and a large abscess, which cultured hemolytic *Staphylococcus aureus*, was drained. Her temperature fell to normal within a few days, but the wound healed very slowly and the granulations lining it continued to look indolent for a long period in spite of careful daily dressings and irrigations with Dakin's solution. Cultures continued to show *S. aureus*, but a secondary contamination of *B. proteus* developed. Because of this wound she was kept in bed until September 10 and in the hospital until October 9. During the 2 weeks before discharge she complained frequently of abdominal discomfort and constipation and she developed a sallow appearance, although her red count remained above 4,000,000 and her hemoglobin above 95%. Examination just before discharge revealed a protruberant abdomen, which was interpreted as obesity, and some edema of the lower legs. The liver could not be felt.

She remained at home for 4 days. During this period abdominal pain rapidly increased, as well as swelling at the ankles, and a feeling of exhaustion. She was readmitted on October 13 with a fever of 101° F., which had been present for the previous 12 hours, and with acute abdominal distention. Roentgen rays of the chest showed a moderate amount of fluid in the left, and Roentgen rays of the abdomen showed gas in both large and small intestine. The following day it was obvious that she was slightly but definitely jaundiced, and that the abdomen was distended by fluid as well as by gas. Cloudy yellow fluid (2500 cc.) was withdrawn by paracentesis, following which it was evident that her liver was enlarged, being palpable 6 cm. below the costal margin and slightly tender. Although somewhat relieved by paracentesis, she became rapidly worse and on October 15 slipped into coma. Urinalysis showed no evidence of ketosis. An electrocardiogram showed nothing of significance and her hemoglobin was 110%, but circulation became progressively worse and, in spite of oxygen and digitalization, she died that evening.

**AUTOPSY.** The significant findings were the presence of many deposits of pigment taking the iron stain in liver, pancreas, bone marrow, thyroid, adrenals, spleen and lymph nodes. There was no pigment in the intestine or skin. The mediastinum showed a normally involuted thymus and no evidence of persistent or recurrent tumor. There was an incidental adenoma of the thyroid. Fluid was present in the abdomen and left thorax and a lobar pneumonia in the right lower lobe.

It was thought that death was related to liver insufficiency secondary to advanced hemochromatosis. Whether the chronic infection in her thigh played a part is questionable. It seems probable that the iron deposits were secondary to her repeated transfusions, since she did not show the skin pigmentation and diabetic syndrome associated with the usual hemochromatosis.

The positive Kline test, present during her year of observation and varying from 3 to 4+ is worthy of special comment. At no time was it accompanied by a positive Wassermann test in the alcoholic antigen or by any clinical evidence of syphilis. Moreover, a therapeutic trial with potassium iodide was without effect on the size of the tumor. Following extirpation of the tumor the blood Kline was still 3+ in December, 1942, but by August, 1943 it had become consistently negative. It is believed that the patient may have had

syphilis, but one can only speculate as to whether the tumor had any influence on the serologic derangement of blood proteins.

With the advantage of retrospection, it seems unfortunate that circumstances prevented earlier operation, in which case the excessive deposition of pigment following the long courses of transfusions might have been avoided.

**Summary.** This patient had a mediastinal tumor which had been present for a number of years, had resisted radiotherapy, but showed no signs of malignancy. During a considerable period of observation, the patient suffered from a profound depression of erythrocyte formation, although leukocytes of bone marrow origin were never deficient in number. The red cells present were not abnormal in size or shape and there was no evidence at any time of chronic blood loss or abnormal erythrocyte destruction. During this period of anemia, reticulocytes were never found on any attempt, except twice when isolated ones were seen within 48 hours of large transfusions. All of the usual therapeutic measures to stimulate red cell formation were without effect. The patient was maintained by transfusions of whole blood and saline suspensions of erythrocytes for 22 months. The mediastinal tumor was removed without difficulty, and she made an uncomplicated recovery. Following removal of the tumor, a sharp reticulocytosis occurred with a resultant restoration of the erythrocyte count to normal, where it remained for a year after operation. During this period she acted on one occasion as a donor for a transfusion, following which her reticulocytes responded normally and her blood count was not conspicuously affected. Ten months after operation she developed an abscess in the thigh which required drainage and healed slowly. Before it had healed completely, 1 year after operation, she rather suddenly developed acute ascites and jaundice, went into coma and died. Autopsy showed widespread hemochromatosis and no evidence of reappearance of the original tumor. The nature of this tumor remains in doubt, though a thymic origin was suggested.

#### REFERENCES

1. CHURCHILL, E. J., and COPE, O.: The Surgical Treatment of Parathyroidism, *Ann. Surg.*, 104, 9, 1936.
2. DIAMOND, L. K., and BLACKFAN, K. D.: Hypoplastic Anemia, *Am. J. Dis. Child.*, 56, 464, 1935.
3. HEUER, G. J., and ANDRUS, W. DE W.: The Surgery of Mediastinal Tumors, *Am. J. Surg.*, 50, 146, 1940.
4. KARK, R. M.: Two Cases of Aplastic Anemia; One With Secondary Hemochromatosis Following 290 Transfusions in 9 Years, *Guy's Hosp. Rep.*, 87, 343, 1937.
5. McEACHERN, D.: The Thymus in Relation to Myasthenia Gravis, *Medicine*, 22, 1, 1943.
6. MACKEY, R.: An Unusual Case of Aplastic Anemia With Organ Changes Resembling Hemochromatosis, *Med. J. Australia*, 1, 172, 1942.
7. OPSAHL, R.: Thymus-Karcinom og Aplastisk Anemi, *Norsk Mag. f. Lægevidensk.*, 2, 1835, 1939.
8. SINGER, K., and DAMESHEK, W.: Symptomatic Hemolytic Anemia, *Ann. Int. Med.*, 15, 544, 1941.
9. WEST-WATSON, W. N., and YOUNG, C. J.: Failed Splenectomy in Acholuric Jaundice, and the Relative Toxemia to the Hemolytic Crises, *Brit. Med. J.*, 1, 1305, 1938.

## USE OF A SIMPLE POSTURAL TEST IN NEURO-CIRCULATORY ASTHENIA

BY MAJ. WILLIAM A. JEFFERS, M.C., A.U.S.\*

CAPT. SAMUEL C. SHEIMAN, M.C., A.U.S.

AND

LT. COL. GEORGE H. O'BRASKY, M.C., A.U.S.

NEUROCIRCULATORY asthenia might be defined as basically a syndrome of dyspnea, palpitation, and precordial pain during rest or upon mild exertion, noted recurringly or persistently by individuals having insufficient evidence of organic cardio-respiratory disease to account for their symptoms. At a processing center for soldiers apprehended absent without leave, we have had ample opportunity to observe the condition, often in its most acute forms. Soldiers were examined during the time that they were rigidly restricted to the post area, and in midwinter when mild respiratory infections were prevalent. At this Post, about 60% of those with potentially disabling medical disorders had neurocirculatory asthenia. Our interest in the associated circulatory phenomena arose from the need to devise an objective test for assistance in determining whether or not these soldiers were capable of performing arduous combat duty overseas, after relatively little further training.

In the past, studies concerning the etiology and abnormal physiology in neurocirculatory asthenia have yielded little that can be expressed in quantitative terms. Lewis<sup>10</sup> has mentioned such etiologic factors as sedentary civilian occupation, inherited weakness, the stress and strain of military life, and infections of various sorts. A large emotional factor has been suspected by many. Cobb<sup>2</sup> has observed, "Of course war is the most stressful phenomenon known . . ." He feels that neurocirculatory asthenia is synonymous with anxiety neurosis.

It has not been possible to link the disorder with any single organic disease. Lewis<sup>10</sup> differentiates it from hyperthyroidism by pointing out that soldiers with neurocirculatory asthenia have cold hands. A diminished vital capacity is not the rule.<sup>21</sup> Among such soldiers examined by one of us (WAJ), the basal metabolic rates and cold pressor tests (*cf.* also Wood<sup>21</sup>) were usually normal, whereas psychiatric consultation frequently revealed evidence of psychoneurosis. Master<sup>12</sup> has reviewed certain measurable tendencies which have been observed: (1) small heart and small cardiac output; (2) inadequate oxygenation of blood; (3) fainting due to inadequate venous return to the heart; (4) abnormalities in electrocardiogram after 2 step exercise.

The studies reported by Starr<sup>19</sup> suggest that certain patients with neurocirculatory asthenia can be shown to have abnormal cardiovascular responses to standing: what he terms "ineoördination of the

\* On leave of absence from the Edward B. Robinette Foundation, Medical Clinic Hospital University of Pennsylvania.

circulation." The official attitude of the Army toward this phase of the problem is indicated by the following directive:

*"Orthostatic hypotension or tachycardia.* The blood pressure and pulse rate will be taken with the individual in the recumbent position and after standing 3 minutes. An increase in a normal pulse rate to 120 beats per minute or more when the individual stands or a decrease of a normal blood pressure (when the individual is recumbent) to values less than 90 systolic and 50 diastolic when the individual stands may be considered evidence of a definite physiologic disturbance—unless the condition is very temporary following an illness, operation, or exhausted state."<sup>20</sup>

We have used a simple modification of a test previously employed in the study of orthostatic hypotension,<sup>9</sup> in an attempt to evaluate the cardiovascular responses of 1052 soldiers. We are aware of the current scepticism toward all types of tests employed to measure physical fitness,<sup>1,4</sup> and have, therefore, used our procedure only as an aid in separating those having transient or borderline circulatory disturbances from those who have persistent or severe abnormalities.

*Indications for Test.* The test to be described was performed on all soldiers in whom the initial physical examination showed one or more of the following: (1) pulse rate of 100 or more; (2) blood pressure of 150 systolic, 90 diastolic, or more; (3) blood pressure of 90 systolic, 60 diastolic, or less; (4) pulse pressure of less than 20 mm. Hg, regardless of the level of systolic and diastolic blood pressure. When time permitted, we performed the initial test after the soldier had been allowed a week to adjust to his new environment. Repeated tests were made in case of doubt, or to evaluate therapy.

*Technique and Rationale of Postural Test.* After the soldier had lain quietly in a comfortably warm room for about 10 minutes, the blood pressure and pulse rate were usually found to be relatively stable, as evidenced by variations of not more than 10 mm. Hg or 10 beats per minute, on two successive readings. Pulse rates were counted for 10 seconds only, in order that rapid changes in both pulse and blood pressure might be determined with ease by a single observer at intervals of 1 minute. Blood pressures were read as the nearest multiple of 5 visible on the aneroid sphygmomanometer. The fourth phase of the Korotkoff sounds (change from clear to muffled) was recorded as the diastolic blood pressure. The subject then stood up beside his bed. Blood pressures and pulse rates were taken immediately, then after 1, 2, and 3 minutes of quiet standing. Thus, for each subject a series of six readings of pulse and blood pressure were obtained.

The oral temperature was not taken routinely, nor was it feasible to require a fixed period of fasting or abstinence from tobacco or coffee. After each test was completed, the soldier was questioned regarding his symptoms and background, and was again examined to rule out organic cardio-vascular disease.

Immediately upon standing, there are circulatory adjustments which accompany the exertion of arising, and others which act in the

same direction to oppose the hydrostatic tendency of the blood to pool inferiorly. Among those accustomed to strenuous exercise these adaptations result in small increases in systolic, diastolic, and pulse pressures and in pulse rate.<sup>5,6,16,18</sup> As the subject continues to stand quietly, one can usually observe fluctuating waves of change from minute to minute. We have used the *maximal* changes from the resting state observed after 1, 2, and 3 minutes of quiet standing as the basis for our interpretation.

Crampton,<sup>3</sup> Schneider and Truesdell,<sup>18</sup> and Starr<sup>19</sup> have reported the slight changes in pulse rate, blood pressure, and pulse pressure which usually occur upon assuming the erect position, and which have been regarded as consistent with a state of good physical training. It should be noted, however, that there were differences in the time of measuring the response to standing among the three reports mentioned above, so that exact comparison of the data of various workers is not possible. Starr<sup>19</sup> has concluded that it is impractical to study incoordination of the circulation upon the basis of measuring only the blood pressure and pulse rate. If one insists upon the standards for normality listed by Starr,<sup>19</sup> we agree that interesting trends will be missed: systolic pressure +15 to -13 mm. Hg; diastolic pressure +22 to -10 mm. Hg; pulse rate +33 to 0 beats per minute. Nor does an exact numerical index, as recommended by Crampton,<sup>3</sup> and by Schneider,<sup>17</sup> allow one to reduce the problem to one of simple arithmetic.

We have devised a classification which takes into account certain well defined clinical conditions, such as tachycardia, bradycardia, hypotension, and hypertension, and expresses the evidence of circulatory incoordination in terms of a tendency toward one or another of these clinical disorders. By so doing, we do not mean to suggest that individuals who demonstrate an abnormal trend may subsequently develop the full-blown clinical condition. On the contrary, the trend may be quite transitory, due to an acute infection, or other cause. Our observations, however, suggest that soldiers who show some of these trends are apt to complain of annoying or disabling symptoms so long as the trend toward incoordination of the circulation persists. Furthermore, our observations indicate that a trend toward the abnormal is apt to be persistent, but may vary in degree from time to time.

The possible changes in blood pressure and pulse rate which might occur with quiet standing are illustrated below: with each type of response in blood pressure, there are five possible trends in pulse rate. A total of 25 reactions, therefore, might conceivably be observed during such a test. The range of pulse rate and blood pressure which we have chosen to indicate each trend is indicated as a part of each definition.

- I. NORMAL (Negative Test). Pulse rate between 60 and 100 while lying or standing. Blood pressure 90 to 145 systolic, and 60 to 85 diastolic, lying, and not over 145 systolic, and 105 diastolic, standing.
- II. TACHYCARDIA. (Systolic, diastolic and pulse pressures remaining normal, cf. I.)



- A. *Persistent*. Pulse rate of over 100, on 2 or more readings while lying or standing. Variation of not more than 20 beats from lying to standing.
- B. *Orthostatic*. Acceleration of more than 20 beats, and tachycardia of 100 or more, as *maximal* effect of quiet standing.
- III. BRADYCARDIA. (Systolic, diastolic and pulse pressures remaining normal, *cf. I.*)
  - A. *Persistent*. Pulse rate of less than 60 on 2 or more readings while lying or standing. No decrease in pulse rate upon standing.
  - B. *Orthostatic*. Decrease of 20 or more beats to less than 60 as maximal effect of quiet standing.
- IV. HYPOTENSION.
  - A. *Persistent*. Blood pressure less than 90 systolic and 60 diastolic on 2 or more readings while lying or standing. Pulse pressure greater than 10 upon standing.
    - 1. With normal pulse rate (*cf. I.*).
    - 2. With persistent tachycardia (*cf. II A.*).
    - 3. With orthostatic tachycardia (*cf. II B.*).
    - 4. With persistent bradycardia (*cf. III A.*).
    - 5. With orthostatic bradycardia (*cf. III B.*).
  - B. *Orthostatic*. Blood pressure less than 150 systolic, and 90 diastolic, lying. Fall in *pulse pressure* to 10 or less during quiet standing. Diastolic blood pressure not over 105.
    - 1. With normal pulse rate (*cf. I.*).
    - 2. With persistent tachycardia (*cf. II A.*).
    - 3. With orthostatic tachycardia (*cf. II B.*).
    - 4. With persistent bradycardia (*cf. III A.*).
    - 5. With orthostatic bradycardia (*cf. III B.*).
- V. HYPERTENSION.
  - A. *Persistent*. Blood pressure of 150 systolic and 95 diastolic or more, lying, or of 150 systolic and 110 diastolic or more, standing on 2 or more readings, *save* for first pressure taken just after standing.
    - 1. With normal pulse rate (*cf. I.*).
    - 2. With persistent tachycardia (*cf. II A.*)..
    - 3. With orthostatic tachycardia (*cf. II B.*).
    - 4. With persistent bradycardia (*cf. III A.*).
    - 5. With orthostatic bradycardia (*cf. III B.*).
  - B. *Orthostatic*. Blood pressure less than 150 systolic or 90 diastolic lying. Increase to 150 systolic or 100 diastolic upon quiet standing—*save* for first pressure taken just after standing.
    - 1. With normal pulse rate (*cf. I.*).
    - 2. With persistent tachycardia (*cf. II A.*).
    - 3. With orthostatic tachycardia (*cf. II B.*).
    - 4. With persistent bradycardia (*cf. III A.*).
    - 5. With orthostatic bradycardia (*cf. III B.*).

From the outline above it is apparent that we have selected more restricted limits for "normality" than most investigators who have employed this type of test. It should be reiterated that it was our purpose to detect soldiers who might develop disabling symptoms as foot soldiers in combat, if they were to be sent overseas after a relatively short period of further training. Many of the soldiers whom we examined already complained of such symptoms to a certain extent, and we observed that, as a group, those who exhibited a positive test had shown little aptitude, physically and emotionally, for combat duty. They might have been able to perform well in some restricted assignment, but they had not shown the aggressiveness and stamina desirable in infantrymen.

TABLE 1.—NUMERICAL INCIDENCE OF TRENDS OBSERVED IN PERFORMING 1294 POSTURAL TESTS UPON 1052 SOLDIERS WITH INITIAL ABNORMALITIES OF PULSE RATE AND BLOOD PRESSURE (those features marked with an asterisk (\*) showed a statistically significant tendency to be associated as entities)

		Blood pressure					
		Normal or negative test	Hypotension		Hypertension		Total
Pulse rate			Persist.	Orthostat.	Persist.	Orthostat.	
NORMAL or Negative test:		367*	2	126	64	45	604
TACHYCARDIA	{ Persistent	151	4	27	68*	33	283
	{ Orthostatic	185	2	148*	36	32	403
BRADYCARDIA	{ Persistent	1	1	1	0	0	3
	{ Orthostatic	1	0	0	0	0	1
TOTAL:		705	9	302	168	110	1294

*Results.* Table 1 shows the incidence of various types of reactions, according to our classification, among the 1294 tests performed upon 1052 subjects. Statistical analysis of this information, based upon calculation of expectancies, shows the following associations to be highly significant: (1) normal blood pressure and normal pulse rate tend to be associated; (2) hypertension, especially if it is persistent, tends to be associated with persistent tachycardia (*cf.* also Fishberg, as quoted by Master<sup>12</sup>); (3) orthostatic hypotension is conspicuously associated with orthostatic tachycardia. Originally, we included in the test the measurement of blood pressure and pulse rate after running 40 paces, followed by compression of both carotid sinuses alternately while the subject stood quietly. After reviewing the first 260 tests so performed, these steps were discarded. No instances of carotid sinus syncope were found, even among those who had fainted repeatedly. Exercise, and the exertion of arising, seemed to exaggerate the trend of the responses observed upon quiet standing, but failed to indicate important trends not shown by the simpler test.

We are well aware that by measuring only the blood pressure and pulse rate one cannot infer with accuracy the behavior of the cardiac output,<sup>19</sup> the venous return to the heart, or the state of the peripheral vascular bed.<sup>9,14</sup> In our experience, however, this test has served as a more reliable indication of the behavior of the individual's usual circulatory responses than the taking of repeated sample readings of pulse and blood pressure, or by performing the cold pressor test on persons showing transient arterial hypertension.<sup>8</sup>

A group of 217 of our subjects were selected at random and retested at intervals of from 1 to 90 days after the initial test. Upon this group of men 493 tests were performed. Analysis of these tests showed a strong tendency for the identical response to be found during two or more tests: identical repetition was observed 78 times, while the chance expectancy of identical repetition was 7.5 times. In addition there was a significant tendency for orthostatic hypertension or persistent hypertension to recur in repeated tests but with variability in the pulse rate response.

The most frequent explanation for a change from a positive to a

negative test seemed to be recovery from a mild infection. Other factors noted were recovery from anxiety, fatigue, and malnutrition, and as the result of physical training for those unaccustomed to exercise. The presence of a mildly positive test is probably not incompatible with arduous physical exertion, if the soldier's will to serve is fundamentally strong, and if he can serve under good leadership.<sup>7,13,15</sup>

In our experience a positive test is compatible with:

- (a) Neurocirculatory asthenia with complicating disease, such as chronic infection. (Frequent.)
- (b) Neurocirculatory asthenia, with marked anxiety, and no demonstrable physical abnormality. (Rare.)
- (c) Chronic infection, exhaustion, slender habitus, or poor state of physical training, without symptoms of neurocirculatory asthenia. (Rare.)

A negative test has been observed with:

- (a) Good health and good state of physical training. (Frequent.)
- (b) Anxiety, mild. (Frequent.)
- (c) Mild, acute or chronic infection. (Rare.)

**Summary and Conclusions.** 1. Because of the need for an objective approach to the evaluation of soldiers about to be dispatched overseas for arduous combat duty, a simple postural test was devised for those showing abnormalities of pulse rate and blood pressure.

2. Standards were chosen on the basis of 1294 tests performed upon 1052 subjects.

3. A positive test can be described as a tendency toward one or another clinical abnormality of pulse or blood pressure.

4. Subjects who exhibit a positive test on one occasion are apt to do so repeatedly, unless there is a manifest change in their physical or emotional states.

5. The test appears to give a more reliable measure of the individual's usual circulatory responses than random sampling of the pulse rate and blood pressure, or application of the cold pressor test<sup>8</sup> to subjects showing a tendency toward hypertension.

6. It is conceded that this type of test can be influenced by emotional factors and is not a proper measure of an athlete's capacity to perform strenuous activity for short periods of time.<sup>1</sup> Conversely, in military medicine, this type of test can be of value in pointing out the soldier having physical disease or emotional instability and deserving of further investigation.

We gratefully acknowledge the assistance of Capt. Albert L. Cooper, M.C., and P.F.C. Norman Ackerman in performing the postural tests; and of Col. Thomas Fitz-Hugh, Jr., M.C., Capt. Hyman I. Segal, M.C., Dr. J. Harold Austin, and Dr. C. C. Wolferth in preparing the report.

#### REFERENCES

1. BROUHA, L., and HEATH, C. W.: *New England J. Med.*, 228, 473, 1943.
2. COBB, S.: *Borderlands of Psychiatry*, Cambridge, Mass., Harvard University Press, 1943.
3. CRAMPTON, C. W.: *AM. J. MED. SCI.*, 160, 721, 1920.

4. FEIL, H., PETTI, M., and PARK, O.: *Am. Heart J.*, **26**, 1, 1943.
5. GAMBILL, E. E., HINES, E. A., and ANDSON, A. W.: *Am. Heart J.*, **27**, 360, 381, 1944.
6. GHRIST, D. G.: *Calif. and Western Med.*, **39**, 161, 1933.
7. GRANT, D. N. W.: *J. Am. Med. Assn.*, **126**, 607, 1944.
8. HINES, E. A., JR., and BROWN, G. E.: *Ann. Int. Med.*, **7**, 209, 1933.
9. JEFFERS, W. A., MONTGOMERY, H., and BURTON, A. C.: *AM. J. MED. SCI.*, **202**, 1, 1941.
10. LEWIS, T.: *The Soldier's Heart and the Effort Syndrome*, London, Shaw & Sons, 1940.
11. MACLEAN, A. R., ALLEN, E. V., and MAGATH, T. B.: *Am. Heart J.*, **27**, 145, 1944.
12. MASTER, A. M.: *Med. Clin. North America*, **28**, 577, 1944.
13. MURRAY, J. M.: *Psychosomatic Med.*, **6**, 119, 1944.
14. NEUMANN, C., LHAMON, W. T., and COHN, A. E.: *J. Clin. Invest.*, **23**, 1, 1944.
15. RAINES, G. N., and KOLB, L. C.: *U. S. Naval Med. Bull.*, **41**, 923, 1299, 1943.
16. ROTH, G. M.: *Am. Heart J.*, **14**, 87, 1937.
17. SCHNEIDER, E. C.: *Mil. Surg.*, **52**, 18, 1932.
18. SCHNEIDER, E. C., and TRUESDELL, D.: *Am. J. Physiol.*, **61**, 429, 1922.
19. STARR, I.: *J. Clin. Invest.*, **22**, 813, 1943.
20. War Department: *Mobilization Regulations 1-9, Standards of Physical Examination During Mobilization*, Par. 63, (r) 26, 1944.
21. WOOD, P.: *Brit. Med. J.*, **1**, 767, 805, 1941.

## SALMONELLA APPENDICITIS

BY A. DANIEL RUBENSTEIN, M.D.

AND

BEN B. JOHNSON, M.D.

BOSTON, MASS.

(From Massachusetts Department of Public Health and the Department of Preventive Medicine, Harvard Medical School)

WHEN signs and symptoms of acute appendicitis occur in conjunction with *Salmonella* infection, the clinical picture may become very confusing. The earlier in the course of the primary disease the acute abdominal manifestations appear, the more perplexing is the diagnosis. In a recent study of 811 *Salmonella* infections<sup>7</sup> this association was noted in 20 cases, 18 of which came to operation. In only one instance had the basic etiology been recognized prior to surgical interference. This study concerns itself with an analysis of these 20 cases.

Pain during the course of *Salmonella* infection is usually the result of involvement of the lymphoid tissue of the small bowel or appendix. Although in the great majority of *Salmonella* cases with gastrointestinal manifestations the abdominal signs and symptoms subside spontaneously, occasionally surgical intervention becomes necessary.

Study of the literature reveals several case reports of acute appendicitis in association with *Salmonellosis*. Widal<sup>8</sup> in 1913 cited the case of a 13 year old girl who developed acute intestinal manifestations, on the 6th day of a *Salmonella* infection. Wilde<sup>10</sup> in 1930 reported on a 22 year old male who was operated upon for appendicitis prior to the recognition of a preëxisting paratyphoid infection. A similar case is described by Rosenthal.<sup>6</sup> His patient, a 14 year old child, had severe abdominal pain for 48 hours. At operation the appendix was acutely inflamed. Enlarged Peyer's patches in the small bowel raised

the question of typhoid fever. However, a culture of the appendix revealed a *Salmonella* organism as the causative agent.

Muller<sup>5</sup> in 1933 reported the case of a 16 year old girl with gastrointestinal symptoms who, on the 3rd day of illness, was operated upon for acute appendicitis. A ruptured appendix was found. Stool cultures were positive for an organism of the *Salmonella* group. Hawkes<sup>2</sup> reported an additional case in a 23 year old male who had definite signs of acute appendicitis 24 hours after the onset of an acute generalized infection. Here, too, a perforated appendix was found at operation. Cultures of the peritoneal fluid and of the stools revealed a *Salmonella* organism.

Mayer<sup>4</sup> reviewed the foreign literature on *Salmonella* appendicitis in 1934. He concluded that *Salmonella* organisms which lodge in the appendix may occasionally, because of mechanical disturbances aroused by the infectious process, give rise to inflammatory reactions of the appendix.

**Summary of Cases.** In practically all the cases quoted in the literature operation revealed an appendix which had either perforated or was acutely inflamed. Of the 18 cases which came to surgery in this series histopathologic examination of the appendix failed to show an acute inflammatory process in 11. Pathologic diagnosis of these cases were as follows: normal appendix, 6; lymphoid hyperplasia of appendix, 3; and chronic appendicitis, 2 (Table 1).

The finding of enlarged mesenteric nodes at operation first called attention to the possibility of *Salmonella* infection in 4 of these patients. Microscopic examination of nodes which were excised in 2 cases revealed an unusual degree of lymphoid hyperplasia.

The pathologic diagnosis for the 7 other cases which came to operation was acute or subacute appendicitis, 5, and gangrenous appendicitis, 2. In spite of a preliminary diagnosis of acute appendicitis, surgery was delayed in two instances until subsidence of the acute abdominal manifestations.

All but three of the *Salmonella* organisms recovered from stool cultures of the 20 patients were typed\* and classified according to the Kauffmann-White schema<sup>3,8</sup> (Table 1). The *Salmonella* types were as follows: *S. paratyphi B*, 6; *S. typhimurium*, 6; *S. newport*, 3; *S. oranienburg*, 1; *S. panama*, 1; and untyped, 3.

Except for the *S. paratyphi B* cases there was no apparent correlation between the *Salmonella* type and the pathologic diagnosis. All 6 *S. paratyphi B* cases were in the group showing no acute inflammation of the appendix. *S. typhimurium* and *S. newport* were isolated from both groups of cases.

With the exception of 5 *S. paratyphi B* infections which occurred in a single epidemic, the remainder were all sporadic cases. In the series of 811 infections previously mentioned<sup>7</sup> *S. typhimurium* and *S. newport* were the types most frequently recovered from sporadic

\* Typing was performed by the Laboratory of the Department of Bacteriology and Serology of the Beth Israel Hospital, New York, N. Y., under the direction of Dr. Erich Seligmann.

TABLE 1.—DATA ON SALMONELLA APPENDICITIS

Patient	Age	Sex	Salmonella type	Pathologic diagnosis	Admission, white blood count (thous. per c.mm.)	Blood agglutination against <i>S. paratyphi B</i>	Duration of positive stools (weeks)	Duration of postoperative temperature (days)
E. C.	15	F	<i>S. paratyphi B</i>	Normal appendix	8.0	Negative	3	22
B. J.	20	F	<i>S. paratyphi B</i>	Normal appendix; lymphoid hyperplasia of a lymph node	5.0	Positive*	4	9
D. P.	8	M	<i>S. paratyphi B</i>	Normal appendix	5.6	Positive*	3	13
E. R.	14	M	<i>S. paratyphi B</i>	Lymphoid hyperplasia of appendix and lymph node	10.3	Positive*	5	8
M. D.	14	F	<i>S. paratyphi B</i>	Chronic appendicitis	10.6	Negative	5	12
J. P.	14	F	<i>S. paratyphi B</i>	Chronic appendicitis	7.1	Positive	3	7
R. M.	9	M	<i>S. typhimurium</i>	Acute appendicitis	17.3	Positive	3	13
B. D.	3	F	<i>S. typhimurium</i>	Normal appendix	43.0	...	1	7
B. F.	10	M	<i>S. typhimurium</i>	Lymphoid hyperplasia of appendix	11.2	...	2	7
L. C.	15	M	<i>S. typhimurium</i>	Subacute appendicitis	10.2	Positive	10	5
A. G.	8	F	<i>S. typhimurium</i>	Acute appendicitis	12.9	...	3	9
D. J.	17	M	<i>S. typhimurium</i>	Not operated upon	...	Negative	3	3
L. S.	14	M	<i>S. newport</i>	Acute appendicitis	15.8	...	6	11
I. D.	9	F	<i>S. newport</i>	Normal appendix	9.2	...	4	4
I. F.	12	M	<i>S. newport</i>	Lymphoid hyperplasia of appendix	11.2	...	5	10
C. J.	42	M	<i>S. oranienburg</i>	Gangrenous appendicitis	14.0	Negative	8	24
M. K.	61	F	<i>S. panama</i>	Not operated upon	18.0	Negative	5	11
L. D.	22	F	Untyped	Normal appendix	5.0	Negative	3	8
A. B.	8	F	Untyped	Acute appendicitis	...	Positive	3	11
A. J.	6	M	Untyped	Gangrenous appendicitis	16.8	Negative	9	

\* Positive in a titer of at least 1 to 40.

cases. Apparently the same general distribution as to *Salmonella* type holds true for the cases complicated by the signs and symptoms of acute appendicitis. There is no one type which showed a marked predilection for the appendix.

The eldest of the 18 operated patients was 42 years of age, while 16 patients were 20 years of age or younger. It has been shown that *Salmonella* infections, with the exception of those due to *S. typhimurium*, are fairly evenly distributed throughout all age groups.<sup>7</sup> It is apparent, both from this series and from cases previously reported in the literature that Salmonellosis complicated by appendicitis tends to occur primarily in the first two decades of life.

The duration of positive stools in the entire group of cases varied from 1 to 24 weeks; 11 patients were infectious for at least 4 weeks. All but 3 of the cases were released from the hospital while still harboring the causative organism.

The agglutination reaction utilizing *S. paratyphi B* as an antigen was performed in 14 of the cases. Positive tests in a titer of at least 1 to 40 were obtained in 7. In our experience, stool cultures are of far greater value than the agglutination reaction in the laboratory diagnosis of *Salmonella* infection.

Of the 18 cases that came to operation, at least one white blood count and a histopathologic examination of the excised appendix was available for 17. As might be expected, the white blood counts of the cases which showed no acute inflammatory changes in the appendix were, in general, lower than those in which the inflammatory process was marked. The lowest admission white count in the latter group was 10,200, while there were 6 cases in the former group with white counts of 10,000 or less. A 3 year old girl with an admission white blood count of 43,000 for which there was no explanation had a normal appendix at operation.

**Case Reports.** CASE 1. E. R., a 14 year old boy, was admitted to the hospital on April 19, 1937 with complaints of nausea and right lower quadrant pain of 4 days' duration. The temperature on admission was 101° F., pulse 110, and respirations 20. Physical examination revealed tenderness in the right lower quadrant where there was moderate spasm. The white blood count was 10,300 with 70% neutrophils. Urinalysis was normal.

Appendectomy was performed 1 hour after admission. A grossly normal appendix was removed. An enlarged mesenteric node was excised for pathologic examination. Postoperatively the temperature remained elevated for 8 days. The white blood count dropped to 7250 on April 24, 1937 (67% neutrophils) and to 6900 on April 26 (54% neutrophils). The blood agglutination reaction was reported positive for paratyphoid B on April 26. Stool culture on May 2, 1937 was positive for *S. paratyphi B*.

*Pathologic Report.* Lymphoid hyperplasia of appendix and lymph node.

CASE 2. L. D., a 9 year old white girl, entered the hospital on October 21, 1942 complaining of abdominal pain, nausea, and vomiting of 24 hours' duration. The pain which had come on suddenly in the mid-epigastrium localized after 24 hours in the right lower quadrant. The temperature was 100.5° F., pulse 102, and respirations 24. Physical examination was negative except for localized tenderness and spasm over McBurney's point. Rectal examination revealed some tenderness on the right side. The white blood count on October 21, 1942 was 9200 (68% neutrophils); urinalysis was negative.

Appendectomy which was performed shortly after admission revealed a normal appendix. There were several enlarged nodes in the mesentery of the terminal ileum. The temperature following operation varied from 101° to 102° F. for 48 hours and remained elevated for a total of 19 days thereafter. The white blood counts from October 21 to October 30 varied from 6200 to 5600. Stool cultures on October 29, November 6 and November 13 were positive for *S. newport*.

*Pathologic Report.* Normal appendix.

CASE 3. L. S., a 14 year old white boy, was admitted to the hospital on October 13, 1942 with complaints of feverishness, chills, and vomiting of 24 hours' duration. Temperature on admission was 100.6° F., pulse 112, and respirations 20. Physical examination was essentially normal. Roentgen ray of the chest on October 14 revealed normal lung fields. Urinalysis was negative.

On the 2nd hospital day there was onset of bloody diarrhea, together with generalized abdominal tenderness. Next day the tenderness became localized in the right lower quadrant. The white blood count at this time was 15,800 with 82% neutrophils. With a preoperative diagnosis of acute appendicitis, laparotomy was performed. The appendix was large, acutely injected and edematous. Postoperatively the temperature rose to 104.6° F. and remained elevated for 3 days. Stool cultures on October 14, October 19, October 28, November 3, November 9, and November 17 were positive for *S. newport*.

*Pathologic Report.* Gross: serosa injected and covered with fibrin; wall edematous and injected; lumen filled with purulent material. Microscopic: mucosa extensively eroded; wall edematous and infiltrated with a large number of neutrophils and showed scattered areas of hemorrhage; vessels engorged.

*Diagnosis.* Acute appendicitis.

CASE 4. C. J., a 42 year old white male, entered the hospital on February 14, 1938 complaining of nausea, vomiting, and severe right lower quadrant pain of several hours' duration. There was a past history of occasional attacks of lower abdominal pain. Temperature on admission was 99° F., pulse 82, and respirations 22. Physical examination revealed marked tenderness and spasm in the right lower quadrant, most marked over McBurney's point. The white blood count was 14,000; urinalysis was negative.

Operation, which was performed 3 hours after admission, revealed a gangrenous appendix. Subsequently temperature rose to 102° F. and remained elevated for 3 days. There was a moderate amount of purulent drainage from the operative wound. The temperature then remained normal until February 17 when it rose to 102° F. and remained elevated for 7 days thereafter. On February 25 patient had frequent watery stools. Stool cultures on March 21, March 26, and April 6 were positive for *S. oranienburg*.

*Pathologic Report.* Gross: markedly enlarged and thickened appendix. Microscopic: partial to complete destruction of the lining mucosa. Inflammatory reaction extends through the wall with destruction of the submucosa and muscularis.

*Diagnosis.* Acute gangrenous appendicitis.

**Comment.** Contrary to the data presented in the literature, in the majority of this series of cases the clinical diagnosis of acute appendicitis was confirmed neither at operation nor by histopathologic examination of the appendix. It must be assumed that lymphoid hyperplasia of the small intestine, appendix, or mesenteric nodes was responsible for the acute abdominal manifestations of these patients. Unfortunately, careful review of the preoperative clinical findings offered no clue which might be helpful in preventing surgical interference. In both Case 1 and Case 2 which are presented as typical of this group, involvement of the lymphoid tissue of the appendix and mesenteric nodes was the most significant pathologic finding.



On the other hand, it must be borne in mind that in some cases the process in the appendix may become very acute. In 7 of our cases the pathologic report was either acute, subacute, or gangrenous appendicitis. Although no perforations occurred in this series, 2 such cases<sup>2,5</sup> have been reported in the literature. Apparently organisms of the *Salmonella* group may produce two strikingly dissimilar pathologic entities in the appendix. Their ability to cause septic lesions elsewhere in the body has been noted previously.<sup>1</sup>

In Case 3, although *Salmonella* infection was suspected prior to the appearance of the signs and symptoms of acute appendicitis, surgery was considered essential. The findings at operation confirmed the diagnosis of acute appendicitis. Obviously, when the symptomatology is suggestive of acute appendicitis, surgery is indicated whether or not a previous diagnosis of *Salmonella* infection has been established.

The period of apyrexia noted only during the course of Case 4 is difficult to explain and merits further comment. Postoperatively the temperature remained elevated for 3 days. Then, after a normal temperature for 2 days, there was a subsequent rise which lasted for 1 week. It is a matter of conjecture whether this patient, subsequent to an operation for acute gangrenous appendicitis, developed a *Salmonella* infection unrelated to the surgical condition. On the other hand, it might be postulated that mechanical disturbance of the intestinal tract set up during the incubation period of a *Salmonella* infection initiated the appendiceal process.

Common to the entire group of cases which came to surgery was the persistence of pyrexia following operation. The duration of fever among the cases varied from 3 to 22 days (Table 1). Apparently an otherwise unexplained persistent postappendectomy fever should raise the question of a missed *Salmonella* infection.

Failure to establish an etiologic diagnosis in cases of *Salmonella* appendicitis may be directly responsible for the spread of infection to contacts. Epidemiologic investigation of hospitalized *Salmonella* cases has, at times, revealed secondary cases among hospital personnel.<sup>7</sup> Family contacts may become infected when patients with positive stool cultures are released from the hospital.

Recent studies suggest that a significant reservoir of *Salmonella* infection exists among the population.<sup>7</sup> Utilizing modern cultural methods, study of appendicitis cases by routine bacteriologic examination of the feces and appendix may be of considerable value in determining how often organisms of the *Salmonella* group are the causative agents. *Salmonella* appendicitis may be more prevalent than is commonly supposed.

**Summary.** 1. When the signs and symptoms of acute appendicitis occur in conjunction with *Salmonella* infection, a difficult problem in diagnosis is presented. This association was noted in 20 cases, 18 of which came to operation.

2. While histopathologic examinations of 11 of these cases failed to show acute inflammation of the appendix, in 7 instances the report was acute, subacute or gangrenous appendicitis. Review of the pre-

operative clinical findings presented no method of differentiating one group from the other.

3. Of the 20 cases, the 17 which were typed were distributed among five different *Salmonella* varieties.

4. *S. typhimurium* and *S. newport* were isolated from cases which showed acute inflammation of appendix and from those which did not. All 6 *S. paratyphi B* cases fell into the category in which involvement of the lymphoid tissue of the appendix or mesenteric nodes was the most significant pathologic finding.

5. Although *Salmonella* infections appear among all age groups, our cases of *Salmonellosis* associated with appendicitis occurred primarily in children and young adults.

6. Unexplained persistent postappendectomy fever should raise the question of an underlying *Salmonella* infection.

7. Recognition of the basic etiology in cases of *Salmonella* appendicitis will aid in the prevention of secondary infections among contacts in the hospital and at home.

#### REFERENCES

1. BORNSTEIN, S.: State of *Salmonella* Problem, *J. Immunol.*, **46**, 439, 1943.
2. HAWKES, S. Z.: Paratyphoid Fever Complicated by Ruptured Appendicitis, *Ann. Surg.*, **110**, 466, 1939.
3. KAUFFMANN, F.: *Die Bakteriologie der Salmonellagruppe*, Copenhagen, Munksgaard, 1941.
4. MAYER, J. B.: Appendicitis Paratyphosa, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, **43**, 550, 1934.
5. MÜLLER, H.: Ueber einen Fall von gangränöser Appendizitis bei Paratyphus, *Breslau, München med. Wochenschr.*, **80**, 1688, 1933.
6. ROSENTHAL, M.: Appendicitis bei Paratyphus, *Zentralbl. f. Chir.*, **57**, 1597, 1930.
7. RUBENSTEIN, A. D., FEEMSTER, R. F., and SMITH, H. M.: *Salmonellosis as a Public Health Problem in Wartime*, *Am. J. Pub. Health*, **34**, 841, 1944.
8. WHITE, P. B.: Further Studies of the *Salmonella* Group, *Med. Res. Council Spec. Rep. Series*, vol. 103, 1926.
9. WIDAL, F.: Sur un travail de M. Walther, concernant un cas d'appendicite paratyphique, *Bull. de l'Acad. de med.*, Paris, **69**, 283, 1913.
10. WILDE, J. F.: Acute Appendicitis Complicated With Paratyphoid Fever, *Brit. Med. J.*, **1**, 16, 1930.

# PROGRESS OF MEDICAL SCIENCE

## DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF  
JOHN H. STOKES, M.D.

HERMAN BEERMAN, M.D., AND NORMAN R. INGRAHAM, JR., M.D.  
PROFESSOR AND ASSISTANT PROFESSORS, RESPECTIVELY, DEPARTMENT OF DERMATOLOGY  
AND SYPHILOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA

---

### BIOLOGIC FALSE POSITIVE REACTIONS TO THE TESTS FOR SYPHILIS

BY HERMAN BEERMAN, M.D.

PHILADELPHIA, PA.

#### PART II\*

**Lymphogranuloma Venereum.** In 1922 Ravaut<sup>245</sup> called attention to the possibility of encountering in patients with lymphogranuloma venereum a transient positive serologic reaction for syphilis which quickly becomes negative without the intervention of antisypilitic treatment. Later (1924), Ravaut, Boulin and Rabeau<sup>246</sup> showed a fleeting positive reaction in 3 of their patients and in 1 of those who, coincident with a fever, had at another time a weakly positive which disappeared definitely without treatment for syphilis. In 1925, May<sup>199</sup> of Uruguay met in a patient with lymphogranuloma venereum a partial positive Wassermann reaction; in 1933 he reported a similar case. He stated in 1940 that a patient with this disease observed by Professor Lamas also had a transient positive reaction. Other cases have been reported by various authors. Freudenthal<sup>92</sup> saw 2 cases among 51 with a weakly positive reaction (Kahn and Citichol), but the Meinicke reaction was negative. Gay Prieto<sup>95</sup> found 1 of 102 cases which gave negative reactions to the Wassermann and Kahn tests, but weakly positive to the Sachs-Georgi and Meinicke tests. On the other hand, other authors like Hellerström<sup>125</sup> (46 cases), Ruge<sup>257</sup> (165 cases), Buske<sup>37</sup> (72 cases) did not find a positive serologic reaction for syphilis among their patients.

De Gregorio<sup>62</sup> found 10 positive reactors among 32 patients, whereas Uribe of Colombia said that 30% of his cases gave positive reactions. Sulzberger and Wise<sup>295</sup> found cases in which the Wassermann reaction was positive for several weeks in the presence of an active lymphogranuloma venereum lesion, and in the absence of syphilitic infection. Frei<sup>816</sup> also found many cases giving transitory false positive Wassermann reac-

\* Part I of this review appeared in the Progress Department of this Journal in the April 1945 number.

tions. Recently, Myerson<sup>219</sup> stated that the Kahn test may be positive early in the course of lymphogranuloma venereum, later becoming negative. Cariola<sup>42</sup> found 27 of 122 cases of lymphogranuloma venereum who showed positive Kahn and Wassermann tests without any signs of syphilis, 24 of whom lost the positive reactivity within 3 months. Knott and his co-workers<sup>163</sup> stated that such false positive reactions occurred in 10 of 31 cases of lymphogranuloma venereum, 10 of 44 cases of chancroid and 2 of 18 cases with heterogeneous genital lesions. Chana<sup>45</sup> of Chile reported that 20% of his 122 cases of lymphogranuloma venereum had positive reactions. He believed that the Kahn verification test was of value since he found a close correlation between the results of this test and the ultimate serologic outcome.

Alteration in the blood proteins has been noted in lymphogranuloma venereum and has been regarded as of diagnostic significance by Jersild,<sup>141</sup> and by Howard, Eisenman and Strauss.<sup>133</sup> After summarizing the observations of a number of investigators and their own work, Rosen, Rosenfeld, Bloom and Krasnow<sup>254</sup> support the diagnostic importance of the lipid-globulin relationship by observations on 116 cases. Hyperglobulinemia occurred in 100% of their cases, and was most marked in the late stage (rectal stricture and esthiomene). They rate this hyperglobulinemia then as a valuable diagnostic lead. The serum lipids were uniformly decreased. In chancroid, for example, there may be an increased globulin content, but there is no decrease in the lipids. These observers found that treatment of the lymphogranuloma venereum brought the lipid values to normal but left the globulin unchanged. Gutman and Wise<sup>112</sup> reporting on the positive formol-gel reaction associated with hyperglobulinemia may be responsible for other somewhat erratic or abnormal findings in the blood of patients with this disease. For example, the high sedimentation rate, often greatly in excess of the level consistent with the degree of obviously active infection; the falsely positive and repeatedly anticomplementary Wassermann reactions reported in the literature may be regarded as phenomena attendant upon the hyperglobulinemia.

Because of a possible relation of the Wassermann and Kahn tests to the globulin fraction of the serum proteins and because Gutman and Williams<sup>111,321</sup> found the Wassermann reaction to be anticomplementary in 22% of 74 Frei positive cases, the results in the Kampmeier, Smith and Larsen<sup>151</sup> cases are of interest. Of the 43 Vanderbilt University Hospital cases, none was found to have anticomplementary Wassermann reactions. Both Wassermann and Kahn tests were negative in 13 cases, and both positive in 9 cases. The Kahn test alone gave negative reactions in 16 additional cases. Both tests yielded a doubtful reaction in 1 case, the Wassermann was negative and the Kahn doubtful in 2 cases, and the Wassermann negative and Kahn positive in 2 cases. In the Nashville General Hospital group of 24 cases, the Wassermann test was negative in 19 instances, positive in 4, and not done in 1. Recently Kampmeier<sup>150</sup> reviewed the cases of rectal stricture treated in the Vanderbilt University Hospital since 1926. Most of these cases were not proven by the Frei test, but analysis of the history and physical findings made it seem reasonable that a certain percentage of them was due to lymphogranuloma venereum. In those selected as probably being cases of this disease, the Wassermann reaction was negative in 29 and positive in 16, 2 were Wassermann and Kahn positive, 6 were Wassermann negative and Kahn positive, 1 was Wassermann doubtful and Kahn positive.

Kampmeier and his co-workers<sup>151</sup> findings do not agree with those of

Gutman and Williams<sup>111</sup> as regards the frequency of anticomplementary Wassermann reactions in lymphogranuloma venereum. (Since this study was completed, they reported an anticomplementary Wassermann and positive Kahn test were found in a patient with bubo and hyperglobulinemia.)

Because of the prevalence of lymphogranuloma venereum in the Negro population in Georgia, Beeson and Miller<sup>16</sup> made a study of the incidence of hyperglobulinemia in 2375 sera, from both the white and the Negro population. The formol-gel test was used to detect the presence of increased globulin. Hyperglobulinemia was found in 0.4% of white males and in 0.6% of white females. In Negroes the respective rates were 5.6 and 8.3%. The difference in prevalence of lymphogranuloma venereum infection is presumed to be the explanation of this racial difference. A higher proportion of cases of hyperglobulinemia found among Negroes with syphilis appeared to be related to the associated presence of lymphogranuloma venereum in those persons.

Jones and Rome<sup>143</sup> studied 79 patients with lymphogranuloma venereum, the majority of whom had total protein values above 8. The mean total protein value was 8.55 and the highest value obtained was 13.33 gm. per 100 cc. Schamberg<sup>265</sup> studied the course of the plasma protein changes in 20 Negroes with early lymphogranuloma venereum treated with sulfanilamide. All of these patients presented, initially, hyperglobulinemia, the globulin reacting toward the normal level as clinical improvement was manifest. Seventeen of the 20 patients in his series had total protein values above 8 gm. at one time or another during the course of their disease. Kampmeier, Smith and Larsen<sup>151</sup> found hyperproteinemia in 62 of the 67 cases of venereal lymphogranuloma which they studied and considered this fact to be of diagnostic value. Kagan<sup>145</sup> found hyperproteinemia in 8 of his 11 cases of lymphogranuloma venereum. The highest total protein in Cardon and Atlas's<sup>406</sup> series of 6 cases of this disease was 11.44 gm. per 100 cc., and the highest globulin value was 7.66 gm. In their earlier paper, Cardon and Atlas<sup>402</sup> commented on the fact that lymphogranuloma venereum was a disease in which biologic false positive serologic reactions and anticomplementary reactions were especially associated with hyperproteinemia. It is interesting that Taussig and Somogyi<sup>299</sup> found that the hyperglobulinemia which is present in most cases of venereal lymphogranuloma occurs also to a marked degree and with high euglobulin values in granuloma inguinale.

May believes<sup>199c</sup> that the positive serologic reactions for syphilis encountered in cases of lymphogranuloma venereum are not false but represent abortive or weak attacks of syphilis due to insufficient quantity of organisms in the inoculum, so that the body defenses are able to keep the syphilitic infection mild. This seems to us to be highly speculative.

**Lupus Erythematosus.** This subject is carefully reviewed by Ambrosetti.<sup>2</sup> Some false positive reactions have been obtained with the various serologic tests for syphilis but the majority of the patients with various phases of this complex have given negative results. Schaumann and Heden,<sup>266</sup> for example, found only 2 definitely positive Wassermanns and another weakly positive reaction among 75 cases. Boas and With<sup>25</sup> found no positive reactions among 146 patients. No positive reactions were encountered in 6 cases by Dudumi and Saratzcano<sup>67</sup> and in 9 by Schönfeld.<sup>267</sup> Gougerot and Burnier<sup>98</sup> noted only 1 positive reactor among 50 patients. Throne's<sup>303</sup> cases, 36 in number, all gave negative reactions except 1 with an antecedent history of venereal disease. Freund<sup>93</sup> col-

lected 23 positive reactions (9%) in a group of 249 patients. Prochazka<sup>242</sup> had 73 patients, of whom 49.3% had an increased anticomplementary capacity. This was present in 8.3% of 6 acute cases. The author believed the cause of this phenomenon resided in the lymphatics. Margarot, Rimbaud and Ravoire<sup>197</sup> observed 24% positive. Kogoj<sup>164</sup> had 8 positive reactors among 132 patients. Carrera<sup>43</sup> found 30% positive serologic reactions, while Pessano<sup>238</sup> noted 8.3% positive results in his 84 lupus erythematosus patients. Ambrosetti's<sup>2</sup> series of 108 patients studied with the Wassermann and Kahn standard tests yielded 4 positive (3.7%), 96 negative (88.8%), 2 doubtful, 1 anticomplementary. In 3 cases the Wassermann was positive but then became negative. Another case with Wassermann negative, Kahn standard negative, gave a Kahn presumptive positive reaction. In another instance the Wassermann was negative but the Kahn standard was doubtful (*i. e.*, --+). Ambrosetti<sup>2</sup> agrees with Pautrier<sup>237</sup> that some patients may simultaneously present lupus erythematosus and either acquired or congenital syphilis.

In this country little attention has been paid to the occurrence of positive serologic reactions to the tests for syphilis or little significance has been laid on their positive outcome. However, recently Sompayrac and Hailey<sup>280</sup> reported such a case with false positive Kahn reaction. In addition Coburn and Moore<sup>49</sup> noted that during life patients suffering from disseminated lupus erythematosus have constantly presented hyperglobulinemia involving gamma globulin. It is believed by some that it is the reaction of this gamma globulin fraction with certain phospholipids which gives rise to false positive Kline and Wassermann reactions.

Our own experience with carefully studied cases of acute and chronic lupus erythematosus would lead us to the conviction that false positive serologic reactions must be indeed rare in these states and when a positive reaction is encountered it probably represents an undiagnosed syphilis or technical error.

**Tuberculosis and Sarcoid.** There is great question whether tuberculosis can cause biologic false positive reactions to the tests for syphilis. This doubtful ability of tuberculosis to cause false positive reactions is confirmed by the literature and the relative infrequency of positive serologic reactions for syphilis among tuberculous groups. Nonetheless, there is a gradually expanding literature on this subject, indicating that some patients with tuberculosis yield positive reactions to the tests for syphilis without their having or having had syphilis.

In 1922, Dulaney<sup>69</sup> found 8 positive Wassermann reactions among 100 tuberculous patients, but did not express himself on the question as to whether or not they actually had syphilis. Kilduffe and Hersohn<sup>158</sup> failed to detect any positive Kolmer or Kline reactions in a group of 200 tuberculous subjects. Stuckey and Huntley<sup>293</sup> felt that the Kahn reaction was not affected by the presence of tuberculosis. Bowman<sup>28</sup> as well as Horowitz<sup>131</sup> also found no influence of tuberculosis, on the reactions to the serologic tests for syphilis. Snow and Cooper<sup>278</sup> likewise could elicit no false reactions using non-cholesterinized antigens, but they found 31% of cases giving + to 2+ reactions with cholesterinized antigen. In the first United States serologic evaluation study,<sup>55</sup> the percentages of positive reactions obtained in 53 cases of tuberculosis were Hinton 5.7, Kolmer 2, Kahn, Kline and Eagle flocculation tests 1.9 each. Parran and Emerson<sup>233</sup> reporting for a committee to study this problem reviewed the earlier literature cited above, mostly denying any significant influence

of tuberculosis on the serologic reactions. Eight out of 458 serums of presumably non-syphilitic individuals from 9 sanatoria gave positive reactions to many tests. Four of these were found to be probably syphilitic, 3 were not available for reexamination and in 1 no evidence of syphilis could be found. These were considered syphilitics, although there is some doubt as to the justification for it. In the remaining 450 serums, 1 positive result was obtained with the Eagle microflocculation test, 4 positives with the Hinton, 1 positive with the Kahn presumptive and 5 positives with the Kline exclusion test. The Kolmer and Kahn standard tests gave negative results. Those tests giving positive results also gave a number of doubtful results. Some positive and doubtful reactions became negative on repetition. Parran and Emerson<sup>233</sup> concluded that "tuberculous toxemia may contribute a confusing factor to syphilis serology. It should not, however, present a major problem in the clinical interpretation of results obtained with carefully conducted serodiagnostic procedures."

Stokes<sup>289b</sup> thought that latent tuberculosis was responsible for false positive serologic reactions. Eagle<sup>71c</sup> reported a case which he concluded was probably technical rather than biologically false. Dunner and Mayer<sup>70</sup> in 1933 found 43 positive reactions to one or all tests used among 1200 patients with pulmonary tuberculosis. These patients also had clinical evidence of syphilis. There were 31 who gave positive reactions to one or several tests and in these there was no history or clinical evidence of syphilis; 12 of these came to autopsy without revealing evidence of syphilis; 5 of the syphilitic patients who came to autopsy likewise had no evidence of syphilis. These authors concluded that positive reactions for syphilis do occur in persons with pulmonary tuberculosis who have neither history nor clinical or autopsy evidence of syphilis. They also observed patients in whom, with the advance of the tuberculosis, negative serologic reactions to the serologic tests for syphilis became positive. The studies of S. Berg,<sup>19</sup> of Warring,<sup>313</sup> and of Sweany<sup>296</sup> indicate that tuberculosis probably causes only an insignificant number of false reactions. Sellek Azzi and Frade,<sup>270</sup> among more than 100 patients with infantile tuberculosis, obtained about 5% false positive serologic reactions for syphilis. The 1941 Washington Serology Conference<sup>243c</sup> showed that among about 59 patients various tests gave 0 to 6.8% non-specificity in tuberculosis of any type. The more widely used tests gave 100% specificity in any type of tuberculosis.

Although sarcoidosis is not generally accepted as of tuberculous origin, discussion of this disease is made here for convenience. The fact that Frazier and Hu<sup>90</sup> were able to isolate *Treponema pallidum* from a subcutaneous sarcoid need not indicate that syphilis is the cause of any type of sarcoid associated with positive serologic reactions. In 1921 Vasek<sup>306</sup> and in 1923 F. Berg<sup>18</sup> reported examples of false reactions in sarcoidosis. Waldenström<sup>309</sup> reported 5 patients with sarcoid with positive serologic reactions, 1 of whom had no clinical, anamnestic or familial evidence of syphilis, but did have increased sedimentation rate and hyperglobulinemia. Waldenström<sup>309</sup> thought this explained the serologic outcome. Reisner<sup>250</sup> found negative reactions in 23 of his 35 cases of sarcoidosis. They were positive in 10 and doubtful in 2 instances. All the positive or doubtful reactions occurred among the 30 Negro patients of this series. He believed that no etiologic significance could be attached to this finding, since prevalence rates<sup>305</sup> show 25 to 30% positive serologic reactions for syphilis among large groups of Negro patients. Antisyphilitic therapy did not

influence the clinical manifestation or course of the disease. Some of the positive cases persisted in spite of intensive and prolonged antisypilitic therapy. Sometimes the reactions fluctuated between positive and negative.

**Acute Exanthemata.** Acute exanthemata have not played an important rôle in the question of biologic false reactions, largely because usually the serologic tests for syphilis are not made on such patients as a routine, and also because in all probability improved serologic techniques have indicated that such diseases as scarlet fever and measles do not often yield false reactions. In fact, Lund<sup>191</sup> by his method of titration of traces of reagin was unable to demonstrate more than the average level of reagin in the blood of patients with scarlet fever.

Scarlet fever has been reported the cause of some false reactions.<sup>206</sup> Landau<sup>178</sup> reported on the Wassermann, Kahn and Sachs-Georgi reactions in the blood obtained from 164 patients, mostly children, with scarlet fever. The Wassermann and flocculation reactions were positive in 1 patient. In 2 patients, the Kahn reaction alone was positive. It became negative in one in the 2nd week, and was still positive in the other in the 3rd week. When the tests were repeated in 2, 3 and 4 weeks, only the Sachs-Georgi reaction was positive in one patient during the 2nd week, but was negative thereafter. The author concluded that scarlet fever is not the cause of non-specific serologic reactions. Monticelli,<sup>209</sup> on the basis of negative results with 364 Wassermann tests (Frankfurt method) on the serums of 150 children with scarlet fever, concluded positive serologic reactions reported in scarlet fever are due to varying sensitivity of the antigens used. He advises standardization of serologic procedure for serologic tests for the various countries.

In 1932 Gunn<sup>110</sup> found occasional false positive reactions in patients with measles and chickenpox. He stated that in acute fevers there is an increase in the normal lipoidophil antibody content of human serum or a transient physical or chemical alteration of its composition which permits complement fixation to occur even in the absence of syphilitic infection. These may be present from the 3rd to the 21st day and rarely persist into the 4th week. His 6 serums from patients convalescing from mumps gave negative reactions. W. Smith<sup>277</sup> found 2 siblings with positive sigma reactions 6 weeks after the onset of mumps. Their parents were negative, and 1 of the patients died of mumps encephalitis. He had a weakly positive Wassermann in blood and cerebrospinal fluid.

In measles, Pockels<sup>240</sup> reported several positive reactions among 206 children studied 1 to 2 weeks after the onset of the disease. Other investigators also noted some false reactions in this disease,<sup>81,110,180</sup> but Eagle<sup>71c</sup> did not find any among 13 cases.

**Rat-bite Fever.** Brown and Nunemaker<sup>35</sup> in 1942 critically reviewed the American cases of rat-bite fever reported up to 1942 and pointed out that adequate proof has been obtained in only few cases, that *Spirillum minus* was the etiologic agent. Of 17 definitely spirochetal cases found in the American literature since 1930, 10 had a positive Wassermann or flocculation reaction. Beeson<sup>15</sup> recently reported 2 more cases due to the spirochete, one of which had several weakly positive Kahn reactions. More recent evidence of the ability of this disease to produce positive reactions is presented by Beeson,<sup>15</sup> by Wooley,<sup>325</sup> and by Taussig.<sup>299</sup> On the other hand, among the older reports, Bayne-Jones<sup>11</sup> deprecated rat-bite fever as a source of false positive reactions. Among 81 patients, 3 of 18 tested yielded positive reactions. Bayne-Jones<sup>11</sup> felt they were syphilitic.



According to Brown and Nunemaker,<sup>35</sup> some cases of rat-bite fever are due to *Streptobacillus moniliformis* (*Streptothrix Haverhillia moniliformis*). Of 8 patients collected from the American literature in whom serologic tests were made, 3 had positive reactions. One of these probably had syphilis, thus leaving only 2 laboratory infections reported by Dawson and Hobby<sup>61</sup> which were insufficiently followed up. Brown and Nunemaker<sup>35</sup> added 8 cases of their own. They made the diagnosis by culture or by a high titer of the antibodies to the streptobacillus. A transient positive reaction was found in only 1 case. These data are insufficient to place this type of rat-bite fever as a real cause of false positive reactions in the serologic tests for syphilis.

Rat-bite fever without specification of cause continues to be reported as a source of false positive reactions.<sup>32,127,206</sup> No reports have been found dealing with the effects of artificial rat-bite fever (Sodoku) used therapeutically, on the development of false positive reactions.

According to Brown and Nunemaker<sup>35</sup> one may conclude that the spirillary form of rat-bite fever is associated in 50 to 60% of patients with a false positive reaction, while in the small number of the streptobacillary cases reported, the false reaction may occur in 37%. Altemeier, Snyder and Howe<sup>1</sup> state that the serologic reactions for syphilis are usually negative in the spirillary form and negative in the bacillary form of rat-bite fever. The fact that penicillin benefits both types does not contribute to the elucidation of the problem of false positive reactions which the other authors cited above have reported as occurring in this disease.

**Relapsing Fever.** Although this is thought to be a rare disease in the United States,<sup>217</sup> it is a frequent cause of false positive reactions to the serologic tests for syphilis. A complete study of the early literature plus their own experience was reported in 1938 and 1939 by Ts'un and Chung,<sup>304</sup> and Chung and Chang.<sup>47</sup> They found that 7.95% of 88 patients had transient positive Kolmer, Kahn or Kline reactions. These reactions became negative usually within 1 to 3 weeks when the temperature was normal. Serums of 29 cases in which intercurrent syphilis was diagnosed were found to be persistently positive. Those from the rest of the cases were uniformly negative. Pai,<sup>229</sup> at about the same time, reported that 7 of 14 cases in his series gave positive Wassermann reactions which became negative when the disease responded to small doses of arsenicals.

**Trypanosomiasis.** Although Landsteiner<sup>179</sup> and his associates found that experimental trypanosomiasis of rats and rabbits gave positive Wassermann and flocculation reactions, it is curious that no recent reference to such an occurrence in patients has been found. This experience is concurred in by Davis. Davis reports that Kelser has developed a diagnostic complement fixation antigen for *T. cruzi*. Kelser stated that "tests of numerous Wassermann-positive sera indicate that no difficulty will be experienced from cross reactions in connection with the two diseases."

**Kala-azar.** There is no unanimity of opinion as to the exact influence of kala-azar on the serologic reactions of the serologic tests for syphilis. Greval and his co-workers<sup>108</sup> believe it is a frequent cause and, in fact, more frequent a cause of positive reactions to the Wassermann test in India than is syphilis itself. Lloyd and his co-workers,<sup>186</sup> however, do not concur. It is interesting to note that an L. E. Napier is involved in the publications of both sides of this question.

**Unclassified Infections.** Natural or induced fever was responsible for 2.2 to 8.9% positive reactions among 46 cases tested in the first United

States Serologic Evaluation Study.<sup>55</sup> Of the so-called "standard" tests, only the Kolmer and the Hinton gave positive results—2.2 and 2.3 % respectively. In the 1941 Washington Serology Conference,<sup>234d</sup> febrile or afebrile intercurrent illnesses yielded mostly 99 to 100 % specificity in the standard tests. Afebrile diseases showed in the standard tests that they were 99.3 to 100 % specific. Corrigan<sup>50</sup> found 3 positive reactions in 3 non-syphilitic cases of endocarditis. On the other hand, Kelson and White<sup>166</sup> state that syphilis of the nervous system and elsewhere has been diagnosed as the primary disease or accompanying condition in subacute bacterial endocarditis because of false positive serologic tests. Brown and Nagle<sup>34</sup> in 1938 found only 1 positive Kahn reaction among 64 patients with tularemia. This disease undoubtedly has little effect on the serologic reactions. Hydatid cyst of the lung has been mentioned in connection with positive reactions.<sup>99</sup> Weil's disease was shown by Rein and Elsberg<sup>248</sup> to be a frequent cause of positive reactions to the tests for syphilis. Among 87 serums, 38 (43.6 %) gave such a reaction. They were usually of low titer. Rein and Elsberg<sup>248</sup> thought that repeated tests in Weil's disease would give a higher percentage of positive reactions. Typhus has also caused biologic false positive reactions. Reynes and Richard<sup>251</sup> reported a case in 1940. Warnecke<sup>311</sup> has also studied this question. Rein and Elsberg<sup>248</sup> studied serums from 104 patients with epidemic and murine typhus and on the basis of single examinations he found 39.4 % positive reactions. Undoubtedly here, too, repeated testing might have raised the percentage of false reactions. No statement is specially made, but it is presumed that Rein's cases were non-syphilitic. Rein and Elsberg<sup>248</sup> also tested serums from 53 patients with filariasis. They noted 11.3 % doubtful or positive results. A number of authors have reported false positive reactions in various diseases, mostly infections in children.<sup>32, 48, 127, 255</sup>

Jaundice of various types has been rated as possibly inducing biologic false positive reactions. Davis and Sidel<sup>59</sup> found 3 positive reactions among 103 patients with jaundice. Rominger and Szego<sup>253</sup> reported a case of catarrhal jaundice with a false positive reaction. In the first United States Serologic Evaluation Study,<sup>55</sup> however, all the more commonly used tests gave no false reactions among 51 cases of jaundice. Other tests gave as much as 2 to 3.9 % positive. Kutzell and Puccinelli<sup>177</sup> observed 15 transient false positive or doubtful positive reactions in 63 patients with infectious hepatitis among allied-military personnel in Sicily. These reactions were noted after the appearance of the jaundice, since the serums were not tested prior to the onset of the jaundice.

**Non-infectious States.** Pregnancy and menstruation have been cited as causing biologic false positive reactions to the serologic tests for syphilis. Spiegler<sup>294</sup> in 1932 found only 0.45 % positive reactions among 6580 patients. In the 1934 serology conference,<sup>55</sup> the "standard" tests, with the exception of the Hinton, gave no such reactions in 54 patients. The Hinton test yielded 109 % positive reactions. Kandler<sup>152</sup> in 1940 concluded from an experience with 10,354 pregnant women, that there is no evidence that pregnancy impairs the sensitivity or specificity of the tests. Ingraham and Mayer<sup>135</sup> likewise, from a small series of carefully studied normal persons, found that the menstrual cycle has no effect on the serologic reactions for syphilis. *Malignant* tumors have given little evidence that they affect the serologic reactions. In this connection, one must remember the frequent association of malignancy and syphilis. The 1934<sup>55</sup> serology conference and the 1941 Washington conference<sup>234d</sup> yielded little to support the idea that tumors cause false positive reactions.

Sorba,<sup>281</sup> however, found that 14.1 % of 262 patients with carcinoma of the cervix gave positive reactions, whereas the usual run of carcinoma patients in the same region gave 1.6 % positives. While these are not claimed to be false reactions, one wonders whether carcinoma of the cervix predisposes to false reactions. Matsumura<sup>198</sup> in 1934 tested the serologic reactions in 397 cases of malignant tumors (336 carcinoma, 61 sarcoma of various parts of the body). The reaction was positive in 13 % of the carcinoma and about 20 % of the sarcoma patients. No clinical evidence of syphilis was found in many of these patients, even at autopsy.

*Horse serum* has been known to produce biologic false positive reactions.<sup>24,91a,126,286,318</sup> Other rarely mentioned causes of reactions are: lead poisoning, acetic acid poisoning, diabetes, drugs (*e. g.*, sulfanilamide), ether anesthesia, repeated blood donation,<sup>300</sup> cadaver blood.<sup>290</sup> The verity of these as producers of false positive reactions is highly problematical.

**Hyperproteinemia.** In connection with certain diseases which yield presumably false biologic reactions, the question of hyperproteinemia has been raised. Certain aspects of this subject have been discussed elsewhere in this review (*e. g.*, lymphogranuloma venereum). A general review of the relationship of hyperproteinemia to biologic false positive reactions of syphilis has been the subject of special study by Cardon and Atlas.<sup>40</sup> They noted that hyperproteinemia, except when caused by dehydration, is associated almost invariably with highly elevated sedimentation rates, even in the absence of fever. Jeghers and Sclesnick<sup>140</sup> observed anticomplementary Wassermann reactions frequently in association with hyperproteinemia, especially in patients with such conditions with lymphogranuloma venereum and multiple myeloma. Cardon and Atlas,<sup>140</sup> comparing the conditions reported with hyperproteinemia with those presumed to give biologic false positive or anticomplementary reactions, suggest that perhaps a common factor is concerned.

While the reasoning of these men is suggestive and the association of hyperproteinemia with biologic false reactions frequent, Cardon's group<sup>40</sup> used criteria of falseness which of themselves are false, namely, the presence of a positive Kahn reaction but negative Wassermann reaction (in 2 cases anticomplementary). They considered 1 patient who had simultaneous positive reactions to both tests as syphilitic. Davis<sup>57</sup> stated that the impression that false positive serologic reactions are often caused by conditions which give rise to a marked hyperglobulinemia is unwarranted. He stated: "Hyperglobulinemia is in general caused by two types of disease: (1) a variety of infections, in which at least part of the increased globulin is antibody; and (2) conditions not especially involving antibodies, such as cirrhosis of the liver, dehydration and multiple myeloma. There is reliable evidence that any member of the second group is associated with these positive tests; it appears reasonable to regard the hyperglobulinemia and the occasional positive reactions of the first group as separate manifestations of the underlying infectious process, rather than to consider one the cause of the other."

Holmberg and Gronwall<sup>129</sup> reported that a peculiar crystallized serum globulin from a patient with an undiagnosed arthritis was reported anticomplementary like other isolated globulins.<sup>58</sup>

**False Positive Reactions in the Cerebrospinal Fluid.** The occurrence of false positive serologic reactions for syphilis in the cerebrospinal fluid has received little attention, although as far back as 1910 Oppenheim<sup>227</sup> reported the first example of angle tumor (pontocerebellar) with positive cerebrospinal fluid Wassermann. In many of the subsequently reported

cases technical error has not been excluded by confirmation of the original positive reaction nor has syphilis always been definitely excluded. Recent authors<sup>71e, 210b</sup> have implicitly relied on the specificity of the cerebrospinal fluid Wassermanns except, perhaps, "in the rare instances in which a syphilitic patient with a positive blood Wassermann develops an acute pyogenic or aseptic meningitis. This phenomenon undoubtedly depends on an alteration of the blood-spinal fluid barrier and a passage of reagin from blood to spinal fluid." Although some authors agree with the idea that false positive reactions represent transfer (filtration) of reagin from the blood, there is evidence that the reagin or antibody is formed within the central nervous system locally.<sup>12b, 93, 144, 214, 319a, b</sup> The chief argument of those who favor the filtration theory is that there is rarely more reagin in the cerebrospinal fluid than in the serum. Wiener and Derby<sup>319b</sup> have shown that while it is true that the reagin content of the cerebrospinal fluid is hardly ever greater than that of the serum, this is not a valid argument for Dujardin's theory.<sup>68</sup> Were the concept of passive filtration correct, a parallel filtration of iso-agglutinins could be expected, but in no case could Wiener and Derby<sup>319</sup> find any iso-agglutinins in the cerebrospinal fluid, even when the reagin titer was equal in blood and cerebrospinal fluid and the iso-agglutinin titer in the blood higher than that of the reagin. Wiener and Derby<sup>319</sup> do not imply that there is never any filtration of reagin from the blood into the cerebrospinal fluid. They further explain the lower titer of reagin in the cerebrospinal fluid on the basis of the usually less poorly developed capacity of the central nervous system to form antibodies, possibly because of its small number of reticulo-endothelial cells. If the Ehrlich and Harris theory<sup>75</sup> of antibody formation in the lymphocytes is correct, Wiener and Derby's contention<sup>319</sup> would still seem to hold.

Further evidence for the idea of local formation of reagin in the central nervous system in neurosyphilis is suggested by the work of Kabat and co-workers<sup>144</sup> who demonstrated a high proportion of gamma globulin in such fluids which could not be explained on the basis of filtration from the blood. The question of faulty absorption of the spinal fluid which may produce a local concentration of the proteins has apparently not been explored. Freund<sup>93</sup> as well as Morgan, Schlesinger and Olitsky<sup>214</sup> have shown that a lower titer of various antibodies develops in passively immunized rabbit's cerebrospinal fluids as compared with the serums. Therefore, aside from cerebrospinal fluids grossly contaminated with positive blood<sup>86, 189, 279</sup> in sufficient quantity to induce a technically false positive reaction in the fluid, fluids otherwise technically correct would rarely, if ever, yield false positive reactions. In spite of this, a large literature has arisen purporting to demonstrate such reactions. Furthermore, to prevent non-specific and prezone reactions in the Wassermann test with sera and spinal fluids, Boerner and Lukens<sup>27</sup> advised the use of egg albumen as a protection protein. Later, however, Boerner, Lucas and Ellis<sup>26</sup> found the addition of egg albumen to cerebrospinal fluid in the Boerner-Lukens method of Wassermann test had a desensitizing effect when pretested complement was used. They recommend avoiding the addition of egg albumen to cerebrospinal fluid if the complement is pretested with the antigen used.

A few reports of false positive cerebrospinal fluids have been made in mumps,<sup>277</sup> in malaria<sup>160, 322</sup> and in neurologic diseases.<sup>64, 142, 181, 200, 213, 256, 271</sup> Kuskic,<sup>176</sup> on the other hand, investigated the frequency with which complement fixation tests for syphilis with cerebrospinal fluid from patients

given malaria treatment for gonorrhea became positive. None of these patients developed positive reactions in the cerebrospinal fluid. He also found that positive Wassermann reactions did not develop in the cerebrospinal fluid of patients with latent syphilis during malarial infection.

Among the neurologic diseases which have been reported as associated with false positive cerebrospinal fluid reactions (with negative blood reactions), encephalitis,<sup>213</sup> post-traumatic convulsions,<sup>142</sup> meningococcus meningitis,<sup>32</sup> pneumonia and meningitis<sup>255</sup> are included. McLean and Munger<sup>200</sup> report 10 cases in which the cerebrospinal fluid gave biologic false positive reactions for syphilis. These consisted of encephalomalacic atrophy, encephalomalacia, streptococcus septicemia, electrical burn, extrathelial panniculitis, cerebrospinal rhinorrhea, skull fracture, concussion, neuritis and multiple sclerosis. The authors produced a positive Wassermann reaction in the cerebrospinal fluid of a dog by injecting intracisternally the fluid from a craniopharyngioma.

Sézary and Terrasse<sup>271</sup> have summarized the literature on false positive reactions associated with tumors of the neuraxis. They added 4 cases of their own to the world's literature (32 in all). Seven of the patients were old syphilitics, but in 25 there was no evidence of syphilitic infection. In most of the cases, the Wassermann was strongly positive. Among 29 cases in which the blood Wassermann was examined, the reactions were positive in 4, slightly positive in 2, and negative in 23. A positive reaction in cases of brain tumor is rare (7 of 40 cases, Vincent<sup>307</sup>). The sites of the tumor seem to have little influence on the outcome of the serologic reaction except that tumors which block the subarachnoid space and cause Froin's syndrome are especially apt to cause this anomaly. Antisyphilitic therapy may often bring about temporary improvement in the brain lesion. The positive reaction in the cerebrospinal fluid in brain tumor is also sometimes accompanied by hyperalbuminosis and hyperleukocytosis. We have seen cases of neuraxis tumors which confirm these findings of a positive Wassermann reaction and excessive protein content of the cerebrospinal fluid. Desneux<sup>65</sup> and, more recently, Cardona<sup>41</sup> have denied that positive Wassermann reactions occur in the cerebrospinal fluid in cases of nervous system tumors in the absence of syphilis.

A most interesting and important contribution to the problem of biologic false positive cerebrospinal fluid Wassermann reactions is that of Scott, Reynolds and Mohr<sup>269</sup> dealing with such reactions associated with meningitis. These workers have shown in a convincing fashion, on the basis of 7 cases of confirmed false positive cerebrospinal fluid Wassermann reactions in non-syphilitic individuals during the course of meningitis (3 tuberculous, 2 meningococcal, 2 aseptic lymphocytic), and on 20 unconfirmed positive cerebrospinal fluid Wassermanns in non-syphilitic patients with various types of acute intracranial disease (technical errors?) that false positive cerebrospinal fluid Wassermann reactions may occur in syphilitic and non-syphilitic patients during the course of pyogenic, aseptic, and tuberculous meningitis, and perhaps other types of intracranial disease. They conclude that the diagnosis of neurosyphilis based on a positive cerebrospinal fluid Wassermann reaction alone is unjustified in patients suffering from meningitis and other acute intracranial disorders until repeated examinations, performed after these processes have subsided, demonstrate the continued presence of reagin. With this view we are in full accord.

Kolmer,<sup>165e</sup> discussing this problem, concludes that cerebrospinal fluids are much less likely than sera to yield these false reactions. This, he

believes, is due in a large part to technical conditions, but it is unlikely that normal non-syphilitic individuals yielding falsely doubtful and positive reactions on the blood also show a similar reaction in the spinal fluid. It is well known that the natural antibodies occurring in the sera of normal individuals do not occur in their cerebrospinal fluids.

**The Possible Causes of the False Positive Reactions.** At the outset of any discussion of this phase of the problem, one may state categorically that there is no definite knowledge as to the mechanism responsible for the production of biologic false positive reactions to the tests for syphilis. Any proposed explanation is countered by evidence "proving" just the contrary. In view of the conflicting and often almost incomprehensible theories of the underlying mechanism of production of not only the false but the true serologic reaction, it is our purpose here only to refer the reader for details to the appropriate publications. Moreover, throughout this presentation, some discussion has been made of some of the points dealing with probable mechanisms.

Davis<sup>57</sup> has conveniently classified the possible causes of biologic false positive reactions as follows: "(a) an antibody identical with the Wassermann antibody produced in syphilis; (b) an antibody differing in some ways from the true Wassermann antibody, but cross-reacting with Wassermann antigen or some component thereof; or (c) physio-chemical changes not involving antibodies, which produce flocculation or complement fixation reactions."

The nature of syphilitic antibodies has been recently discussed in detail by Eagle,<sup>71a,d,e</sup> Eagle and Hogan,<sup>72</sup> Witebsky,<sup>324</sup> Beck,<sup>12c</sup> Kolmer,<sup>165a</sup> Davis,<sup>57</sup> Ratcliffe,<sup>244</sup> and Sachs.<sup>259</sup> The review of this subject by Davis<sup>57</sup> and his proposals for future study of the fundamental processes involved in the problem of biologic false positive reactions are worthy of extended study.

**Spirochetal Antigens in the Serum Diagnosis of Syphilis.** Antigens prepared from cultures of *Treponema pallidum* have recently aroused considerable interest and a hope that they might serve as a specific means of differentiating true from biologic false positive reactions to the sero-diagnostic tests for syphilis, as well as help to explain the basis for these reactions. This work, revived in this country by Erickson and Eagle<sup>78</sup> has been thoroughly restudied by Kolmer and his group in a series of exhaustive publications.<sup>165a,f,g,h,i,169a,b,172</sup> Unfortunately the use of spirochetal antigens does not supply the answer to the specific *versus* the non-specific reaction question. But, because of the fundamental problems involved, it is proposed to review the significant facts regarding spirochetal antigens.

Antigens prepared from cultures of *T. pallidum* were first employed in 1912 by Noguchi,<sup>225</sup> and Craig and Nichols,<sup>53</sup> and in 1913 by Kolmer, Williams and Laubaugh.<sup>172</sup> At that time these antigens were found to be inferior in sensitivity to alcoholic extracts of beef heart reinforced with cholesterol in the Wassermann test. In 1929 the work of Gaeltgens<sup>94b,c</sup> and Gaeltgens, and Otto<sup>94a</sup> renewed interest in spirochetal antigens, prepared from cultures of the Reiter strain of *T. pallidum*. This was followed by a large literature on the use of this antigen, which was commercially available in Germany as "palligen" and other spirochetal antigens. For a complete critical review of this literature the reader is referred to the excellent paper by Kolmer.<sup>165f</sup> Kolmer, Kast and Lynch<sup>169b</sup> found, however, that antigens prepared from cultures of *Treponema microdentium* and *T. macrodentium* are capable of fixing complement with syphilis reagin just as well as those prepared from cultures of various strains, of *T. pallidum*,

including the Reiter strain. That is to say, complement fixation reactions with spirochetal antigens in syphilis are of a group character. Kolmer, Kast and Lynch<sup>169b</sup> also found the same to be true of agglutination of these spirochetes by normal and syphilitic serums. Kolmer and Kast<sup>168</sup> suspect on the basis of cultural characteristics that the Reiter strain may not be *T. pallidum* at all.

In spite of the claims that spirochetal antigens are specific, it has been well demonstrated that antigens prepared of cultures of alleged *T. pallidum* are capable of giving a varying percentage of non-specific or falsely positive complement-fixation reactions with the sera of non-syphilitic individuals.<sup>169a</sup> In a total of 36,255 tests employing "palligen" these have varied from 0.4 to 3.4%.<sup>165ag</sup> In fact, Erickson and Eagle<sup>78</sup> reported the 3.4% false positives in the serums of 528 non-syphilitic individuals although none were observed in the serums of 15 additional individuals who were normal.<sup>72</sup> In the 1941 Washington Serology Conference,<sup>234d</sup> Richter found that the Kolmer simplified tests conducted with an antigen of the Reiter strain gave 6.3% positive or doubtful reactions with the serums of normal individuals and non-syphilitic patients, excluding those with leprosy and malaria. In the same survey Eagle<sup>71</sup> found 1.9% positive or doubtful reactions on the same group with a spirochetal antigen likewise prepared of the Reiter strain. With both antigens, the percentage of these falsely positive reactions with the serums of non-syphilitic individuals was higher in the case of those with febrile intercurrent diseases, tuberculosis and malignant disease than in normal individuals. The antigen likewise yielded high percentages of positive reaction in serums from patients with malaria and especially leprosy just as non-specific reactions occur in the serums of patients with these diseases when tested with the Wassermann or flocculation tests. In the Washington Conference Richter reported 57.6% positive or doubtful reactions with the serum of lepra patients tested by the Kolmer simplified method using tissue antigen and 27.1% positive or doubtful reactions with the Kolmer spirochetal antigen. The Eagle Wassermann test gave 39.8% and his spirochetal antigen 20.6% positive or doubtful reactions. These figures argue very potently against Eagle and his colleagues' claims that the use of spirochetal antigens will identify as biologic false reactions the positive Wassermann and flocculation reactions encountered in leprosy and malaria. Kolmer interprets these results to mean that in the serums of some non-syphilitic human beings there is a natural spirochetal antibody capable of yielding falsely positive reactions to the complement fixation as well as flocculation procedures, not only with suspensions of cultures of "alleged *T. pallidum* but with other spirochetes as well with special reference to *T. microdentium* and *T. macrodentium*." While this natural antibody may occur in serums it does not occur in the cerebrospinal fluids of non-syphilitic persons.<sup>169a</sup> This is in keeping with the well-known fact that natural antibodies like antitoxins, agglutinins, etc., commonly present in normal serums, do not occur in normal cerebrospinal fluids. Accordingly Richter and Eagle did not find any non-specific or falsely positive complement fixation reactions with cerebrospinal fluids of non-syphilitic individual tests with spirochetal antigen in the Washington survey.

Kolmer, Kast and Lynch<sup>169a</sup> also found that the acquired antibody in syphilis is more likely to give positive complement fixation reactions with antigen prepared of virulent *T. pallidum* (Nichols-Hough strain) recovered from acute testicular syphilomas of rabbits than with antigens prepared of cultures of non-virulent *T. pallidum*. Technical difficulties of securing

the tissue spirochetes free of cellular débris make it unlikely that tissue spirochetes can be used on a large scale. A culture of virulent *T. pallidum* has not as yet been obtained<sup>168</sup> even by the newer methods of chick embryo<sup>228</sup> or tissue culture.<sup>168,320</sup>

The question is unanswered as to whether or not spirochetes contain an ubiquitous lipid also present in alcoholic extracts of beef heart with the result that the various serologic tests are due to spirochetal antibodies as maintained by Eagle and Hogan.<sup>72</sup> Kolmer, Kast and Lynch<sup>169</sup> showed by absorption experiments that the reagin responsible for the Wassermann and flocculation reactions in syphilis is different from the antibody producing positive reactions in these tests with the spirochetal antigen. This view is affirmed by Kroó, Schultze and Zander,<sup>175</sup> Gaechtgens,<sup>94e</sup> and by Beck.<sup>12c</sup> Beck reached this conclusion concerning the independence of the 2 types of reagin by observing that the absorption of syphilitic serum with Wassermann antigen removed the reagin but not the complement-fixing antibody or agglutinin for the Reiter strain of *Spirochaeta pallida*. On the other hand, absorption with spirochetes removed all of the reagin. Absorption with an alcoholic extract of the Reiter strain of spirochetes removed the reagin but not the spirochetal antibodies. This showed a relation between the lipids, of the spirochetes and the lipids of the Wassermann antigen (alcoholic extract of heart). Eagle and Hogan<sup>72</sup> have reported that absorption of human syphilitic serum with beef heart lipids removed all of the reagin but not the spirochetal antibodies. This accords with the experience of Kolmer<sup>165r</sup> and Beck.<sup>12c</sup> But Eagle and Hogan<sup>72</sup> reported that absorption with the Reiter strain of spirochetes ("palligen") removed not only the spirochetal antibodies but the reagin as well, in contrast with the results of Beck and Kolmer. As a result of their experiments Eagle and Hogan<sup>72</sup> concluded that spirochetes contain an ubiquitous lipid, also present in alcoholic extracts of beef heart and that the Wassermann, flocculation and spirochetal complement fixation reactions are due to spirochetal antibodies. Kolmer has disagreed with this view and in addition maintains that immunization of rabbits with living and heat-killed strains of *S. pallida* (Nichols-Hough; Noguchi; and Kroó) as well as with *T. microdentium* and *macrodentium* produced large amounts of spirochetal antibodies but not the reagin "lipoid antibody."<sup>169a</sup> Kolmer considers the question whether rabbits given injections of tissue lipids produce reagin and spirochetal antibodies as undecided.<sup>13,72,165a,260</sup> Beck<sup>12c</sup> furthermore noted that when human syphilitic serum is heated at 63° C. for 30 minutes the spirochetal antibody is not destroyed but the Wassermann reagin is. Eagle and Hogan<sup>72</sup> found no difference in thermoresistance while Kolmer, Rule and Trist<sup>171</sup> found that heating serum 30 minutes at 62° C. results in a definite loss of Wassermann antibody. Kolmer found a lesser loss in the case of the spirochetal antibody. In the case of normal rabbit serum, Kolmer found striking differences in resistance to heat between the substance yielding positive Wassermann reaction and spirochetal antibody. The former is destroyed at 62° C. while the spirochetal antibody is resistant. It is possible that this Wassermann reactive substance in normal rabbit serum may not be identical with human syphilitic reagin. It is concluded that the preponderance of evidence favors independence of the spirochetal antibody and syphilis reagin.

The mode of action and the chemical nature of spirochetal antigen is unknown. It is probable, according to Kolmer and his associates<sup>172</sup> and to Beck,<sup>12c</sup> that the lipids of *T. pallidum* are important in complement fixation by the Wassermann reagin. Whether spirochetal antibody



reacts with them is unknown; but it has been suggested that it fixes complement with some other constituent of spirochetes of a non-protein nature.<sup>169b</sup>

The value of spirochetal antigens as a differential test seems to the Reviewer to be questionable. In the Washington Survey, Richter, using Kolmer's simplified test with tissue or lipoidal antigen had a sensitivity rating of 74.1% and the Kolmer spirochetal antigen 70.6%. The rating for the Eagle Wassermann test was 59.2% and for his spirochetal antigen 75.9%. Kolmer also found that a mixture of spirochetal and tissue or lipoidal antigens was more sensitive in complement fixation tests with syphilitic sera than spirochetal antigen alone, but less sensitive than tissue or lipoidal antigen alone. The mixture has also given a smaller percentage of non-specific or falsely positive reactions with normal serums than the spirochetal antigen alone.

**Verification Tests.** Shortly after the complement fixation and flocculation tests were found to be non-specific, a number of laboratory procedures were devised to differentiate between true and false positive reactions. Hecht<sup>121</sup> in 1914 proposed the first of these so-called verification or confirmation tests. This was followed in 1921 by that of Wassermann<sup>314</sup> which was based on an alleged separation of antibody from antigen by filtration. Witebsky<sup>324</sup> in 1933 obtained purified antibody from a malarial serum as well as from syphilitic serum by a method of heat dissociation but he failed to recover any from certain other false positive serums. Others have also proposed differentiation tests which have proven to be of little practical value.

In 1940, R. L. Kahn<sup>146</sup> showed that: (1) Serums from syphilitic persons giving positive reactions with a diagnostic test show by means of a special procedure a tendency toward marked precipitation at 37° and little or no precipitation at 1° C. The procedure is similar to that of the Kahn test. (2) Serums from apparently normal animals and from presumably non-syphilitic persons giving positive reactions with a diagnostic test show by the same procedure a reverse tendency, namely, marked precipitation at 1° and little or no precipitation at 37° C.

These observations suggested the practical utilization of this procedure. Thus, when a serum gives a positive reaction with a diagnostic test and this reaction is suspected of being a false positive, the serum is examined with this procedure at 37° and 1° C., respectively. If precipitation is found to be marked at 37° and is negative or practically negative at 1° C., the probability is that the diagnostic test gave a correct reaction. If, however, precipitation is found to be marked at 1° and is negative or practically negative at 37° C., the probability is that the diagnostic test gave a false reaction.

The term "verification test" has been applied to this differential temperature procedure. The test is reported positive or negative, depending on whether the serum tested gives more marked precipitation at 37° or at 1° C. In the case of strongly positive serums, the degree of precipitation is not affected by temperatures of 37° or at 1° C., unless they are first diluted with physiologic salt solution. The extent of dilution necessary is determined by the quantitative Kahn test. After thus reducing the serums from strongly to weakly positive, the differences in the results at the two temperatures become evident.<sup>149</sup>

Application of the Kahn differential temperature verification test to the problem of the biologic false positive reaction has led to a variety of differing opinions. Chargin and Rein<sup>45</sup> in their appraisal of this test on

clinical and serologic grounds on 1565 patients with various conditions comprising syphilis and various dermatoses, questionable conditions, pregnancy, contagious conditions, found that among 349 syphilitic patients who had received varying amounts of treatment, the verification tests gave the syphilitic type of reaction in 100% of those with strongly positive serodiagnostic reactions, in 76.5% of those with weakly positive reactions and in 40.2% of those showing doubtful reactions. There were no reactions of the syphilitic type in the patients with negative serodiagnostic reactions. The general biologic type of reaction in the group with negative serologic reactions was 7.1% and in the group with doubtful serologic reactions 12.1%. In the non-syphilitic groups a varying percentage of syphilitic and general biologic types of reaction was noted. It would appear therefore that strongly positive serums regularly give the syphilitic type of reaction but weakly positive serums, syphilitic or not, tend to give the other type of reaction. Green and Forster<sup>100</sup> have indicated from their study that the usefulness of the verification reaction lies in the diagnosis of syphilis no less than in the recognition of falsely positive reactions. Beveridge<sup>21</sup> also felt that the verification test gives a great increase in sensitivity apart from its verification aspect. In 268 patients with pinta, all of whom gave strongly positive serodiagnostic reactions, Chargin and Rein<sup>46</sup> found 83.9% gave a syphilitic type of reaction to the verification test. Briceno Rossi,<sup>31</sup> however, found that in general the test gave a syphilitic type of reaction in pinta and yaws. The syphilitic type of verification reaction has been reported in some serums from patients after vaccination (Lubitz,<sup>130</sup> Lynch, Boynton and Kimball;<sup>193</sup> Thomas and Garrity<sup>302</sup>). Of 30 lepers Briceno Rossi<sup>31</sup> found 19 to give negative verification reactions; 4 positive at 1° C., and 37° C.; 3 gave the syphilitic type and 4 the general biologic type of result. Chargin and Rein<sup>46</sup> found essentially the same degree of unreliability of the test in leprosy. The test has even been accepted and recommended for routine use in malarial districts.<sup>44,138</sup> Kahn<sup>146</sup> soon recognized the shortcomings of his heat test and in 1942 proposed a new verification method. This consists in carrying out a standard Kahn test parallel with a similar test in which the antigen suspension is prepared by mixing the antigen with 2.5% sodium chloride solution instead of the 0.9% salt solution, and also one in which the serial dilutions are made with distilled water. A higher quantitative titer on serial dilution with 2.5% salt concentration than 0.9% salt concentration denotes a general biologic (non-syphilitic) type of reaction. In the presence of the latter type of reaction the titer with serial dilutions of distilled water is still higher than that with the serial dilutions of 0.9% salt solution. This type of verification test has not had wide usage.

Kahn<sup>146d</sup> apparently induced by Chargin and Rein's<sup>46</sup> evaluation of the heat differential test has added a third test to the second "salt dispersibility technique" which he has designated "Method B." This consists of performing the standard Kahn test as usual with the exception that, after the 3 minutes shaking period, sodium chloride solution of 2.5% concentration instead of 0.9% is added to the tubes in the regular amounts of 1, 0.5 and 0.5 cc., respectively. If a physician submits a specimen for verification the following procedure is followed: (1) A standard Kahn test is performed; (2) "Method B" is carried out; (3) the salt dispersibility technique is done. In the case of weakly positive and negative reactions, the "heat differential" test is applied while in the case of strongly positive results, the "triple quantitative technique" is employed. An excellent critique of the so-called "verification" tests with particular reference to

the various Kahn tests is given by Mohr, Scott, Hahn, Clark and Moore.<sup>207</sup> One must agree with these authors—that the “serologic phenomena noted by Kahn are of the greatest importance for further detailed scientific investigative study. It is clearly of fundamental concern to determine whether the positively reacting substance occurring in certain (perhaps all) normal human beings or produced after intercurrent infections or other stimuli, is qualitatively identical with the reagin produced in syphilis. To apply these phenomena to a diagnostic test, designated by so great an authority as Kahn as a “verification test,” is, however, distinctly premature on the basis of present information.”

Rytz<sup>258</sup> proposed a differential test in 1939 involving the principle of removing the bulk of serum protein by precipitation with 2% copper sulfate solution and leaving in solution the reacting substance of syphilitic serum. In spite of repeated progress reports by Rytz,<sup>258</sup> no concerted attempt to verify the performance of this procedure has developed.

Neurath and his associates<sup>223</sup> at Duke University in an extensive investigation directed toward the development of a serodiagnostic method for the differentiation between syphilitic and non-syphilitic sera, made observations which indicate that in the 2 groups of sera the reactive antibodies differ from each other in certain significant respects. Based on the previously reported work which showed that even in strongly reactive syphilitic sera the antibodies constitute but a minute fraction of the total proteins and that isolation by specific flocculation with lipoidal antigen yields extremely low recovery of the purified product, a practical approach to the problem was attempted by this group based on non-specific methods of characterization and fractionation of the sera. Results with electrophoresis, fractionation, inhibition, and redispersion, heat stability and adsorption in calcium phosphate indicate that the antibodies of truly syphilitic serums reactive with lipoidal antigen, differ from those of biologic false positive serums in certain chemical and immunologic respects. These investigators are exploring the possibility of adapting these findings to the development of a practical method of differentiating true from false positive reactions to the tests for syphilis. Rein and Pillemer<sup>247</sup> tried an “inhibition procedure” for differentiating true from false reactions but they found the method to have definite limitations.

**Requirements of a Satisfactory Differential Test.** Rein and Elsberg<sup>248</sup> have outlined under the following heads the criteria a verification procedure must fulfill before it can be considered practical.

- “1. Serums from syphilitic individuals with positive serologic tests should always give a syphilitic type of verification reaction.
- “2. Serums from non-syphilitic individuals with positive serologic tests should always give the false positive type of verification reaction.
- “3. The diagnosis of syphilis should be established in persons who consistently give the syphilitic types of verification reaction on repeated examination.
- “4. The diagnosis of syphilis should be excluded in persons who consistently give the biologic false positive (non-syphilitic) type of verification reaction on repeated examination.”

Whether or not newer differentiating methods will yield reliable information is a question. In 1943 Kahn<sup>146f</sup> still maintained that with his verification tests their greatest value lay “in the investigation of the specificity of positive serodiagnostic reactions in such cases in which all clinical indications point to the absence of syphilis.” Rein and Elsberg<sup>248</sup> are

not so certain that too much confidence can be "placed in the verification test results in those individuals whose syphilitic status is in doubt." The Reviewer's limited experience agrees with this latter viewpoint.

**Management of a Suspected Biologic False Positive Reaction.** Since there is no satisfactory single procedure or combination of laboratory procedures as yet available to differentiate with certainty between true and false reactions to the tests for syphilis, various compromise clinical and laboratory work-ups have been suggested. In 1926 Stokes<sup>289a</sup> cited a series of 22 procedures which might have to be invoked in reaching a decision as to whether or not a patient has syphilis. In 1939 he proposed a scheme for the checking of a positive serologic test report.<sup>289b</sup> This was followed in 1940 by a brief outline of a procedure for the attempted differentiation of these two types of reactions by Moore<sup>210a</sup> and later this was elaborated by Moore, Eagle and Mohr.<sup>211</sup> Other, but somewhat similar, methods of procedure were suggested by Harrison and Osmond,<sup>116</sup> by Kolmer,<sup>165f</sup> by Rein and Elsberg,<sup>248</sup> and by Davis.<sup>57</sup> All these schemes have the same defect; none of them even if followed precisely will really differentiate a true from a biologic false positive reaction. Since, however, they represent the best method of approach to the problem we possess, the method<sup>211</sup> is outlined briefly. For details, the reader is referred to the original sources.

Moore and his associates<sup>211</sup> have suggested the following procedures when biologic false positive serologic tests for syphilis are suspected: careful history; careful physical examination for evidences of acute infection preceding the questionable serologic test, with special reference to lymph nodes, spleen and lungs; search of blood smears for malarial parasites; blood smears for infectious mononucleosis; blood test for heterophil antibody (the Paul-Bunnell test, which is specific for infectious mononucleosis); determination of the sedimentation rate; repetition of the serologic test for syphilis by several different techniques and in several different laboratories; performance of a "verification test;" testing the patient's serum by complement fixation with spirochetal antigen; testing the patient's serum with wholly non-specific antigens such as those prepared from bacteria; prolonged serologic follow-up; examination of the members of the family and sexual contacts; examination of the cerebrospinal fluid, if a decision cannot be reached earlier. These authors consider the provocative procedure worthless. They advise withholding antisyphilitic treatment unless and until the diagnosis of syphilis is proved.

The occasional occurrence of false positive reactions should not lead to wholesale condemnation of the serologic tests for syphilis. The following quotation from Harrison and Osmond<sup>116</sup> is a sound evaluation of the present status of these procedures.

"In 1918 the Medical Research Committee's (now the Medical Research Council) Committee on the Standardization of Pathological Methods said:

*"In the opinion of the Committee there is no process of biochemical diagnosis that gives more trustworthy information or is liable to a smaller margin of error than the Wassermann test when it is performed with completeness and with proper skill and care."*

"This is probably as true today as it was when written a quarter of a century ago, but it is equally true that no group of tests has given rise through unskillful performance and through inadequate appreciation of their limitations, to more unhappiness than have the serum tests for syphilis."

## REFERENCES

- (1.) Altermeier, W. A., Snyder, H., and Howe, G.: J. Am. Med. Assn., 127, 270, 1945.  
 (2.) Ambrosetti, F. E.: (Estudio clínico sobre 156 observaciones), "El Ateneo" Libr. Científica y Literaria, Buenos Aires, 1942. (3.) Arnold, H. L., Jr.: Personal communication. (4.) Arthur, R. D., and Hale, J. M.: Mil. Surg., 92, 53, 1943.  
 (5.) Badger, L. F.: U. S. Pub. Health Rep., 46, 957, 1931. (6.) Barnard, R. D.: Illinois Med. J., 77, 78, 1940. (7.) Barnes, M. E., Borts, I. H., Miller, C. I., and Spanswick: J. Iowa Med. Soc., 33, 500, 1943. (8.) Barnett, C. W., Jones, R. B., and Kulchar, G. V.: Proc. Soc. Exp. Biol. and Med., 33, 214, 1935. (9.) Barnett, C. W., Kulchar, G. V., and Jones, R. B.: Am. J. Syph., Gon. and Ven. Dis., 22, 72, 1938. (10.) Bay, A. P., and Sankstone, M. I.: J. Am. Med. Assn., 115, 475, 1940. (11.) Bayne-Jones, S.: Internat. Clin., 3, 235, 1931. (12.) Beck, A.: (a) J. Path. and Bact., 44, 399, 1937; (b) J. Ment. Sci., 84, 370, 1938; (c) J. Hyg., 39, 298, 1939. (13.) Becker, F. T.: J. Invest. Dermat., 2, 125, 1939. (14.) Beerman, H.: (a) Am. J. Syph., Gon. and Ven. Dis., 20, 165, 296, 1936; (b) Am. J. Med. Sci., 205, 611, 1943. (15.) Beeson, P. B.: J. Am. Med. Assn., 123, 232, 1943. (16.) Beeson, P. B., and Miller, E. S.: Am. J. Med. Sci., 207, 643, 1944. (17.) Benedikt, I.: Ann. Pædiat., 157, 340, 1941. (18.) Berg, F.: Hygiea, 85, 401, 1923. (19.) Berg, S.: Quart. Bull. Sea View Hosp., 4, 402, 1939. (20.) Bernstein, A.: (a) J. Clin. Invest., 13, 419, 1934; (b) Am. J. Med. Sci., 196, 79, 1938; (c) Medicine, 19, 85, 1940. (21.) Beveridge, W. J. M.: Edinburgh Med. J., 50, 344, 1943. (22.) Blumenthal, F., and von Malinicrodt-Haupt, A.: Jadasohn Handbuch der Haut. u. Geschlechtskrankheiten, 15 (Teil 2), 416, 1929. (23.) Boas, H., and Neergaard, I. S.: Dermat. Ztschr., 71, 6, 1935. (24.) Boas, H., and Tølbøl, G.: Dermat. Wehnschr., 94, 173, 1932. (25.) Boas, H., and With, K.: Ann. dermat. et syph., No. 12, p. 622, 1922. (26.) Boerner, F., Lucas, M., and Ellis, A. E.: Am. J. Med. Tech., 8, 118, 1942. (27.) Boerner, F., and Lukens, M.: J. Clin. Path., 11, 71, 1941. (28.) Bowman, A. K.: Lancet, ii, 1288, 1923. (29.) Brants, J.: Dermat. Wehnschr., 95, 1688, 1932. (30.) Brezeale, E. L.: (a) Southwest. Med., 25, 321, 1941; (b) Ibid., 25, 362, 1941; (c) Ibid., 25, 393, 1941; (d) Ibid., 26, 13, 1942; (e) Ibid., 26, 47, 1942. (31.) Briceno Rossi, A. L.: Rev. San. y Asist. Soc., 8, 153, 1943. (32.) Bridgeman, M. L., and Jacobson, L. D.: Northwest. Med., 40, 325, 1941. (33.) Brittingham, J. W., and Rosen, S. F.: Am. J. Syph., 16, 403, 1932. (34.) Brown, E. C., and Nagle, N.: J. Lab. and Clin. Med., 23, 1310, 1938. (35.) Brown, T. McP., and Nunemaker, J. C.: Bull. Johns Hopkins Hosp., 70, 201, 1942. (36.) Burney, L. E., Mays, J. R. S., and Iskrant, A. P.: Am. J. Pub. Health, 32, 39, 1942. (37.) Buske: Cited by May, 1940. (38.) Butt, E. M., and Foord, A. G.: J. Lab. and Clin. Med., 20, 538, 1935.  
 (39.) Capelli, E.: Giorn. Batteriol. e Immunol., 22, 425, 1939. (40.) Cardon, L., and Atlas, D. H.: (a) Arch. Int. Med., 71, 377, 1943; (b) Arch. Dermat. and Syph., 46, 713, 1942. (41.) Cardona, F.: Riv. di pat. nerv., 49, 77, 1937. (42.) Cariola, P. C.: Rev. méd. de Chile, 69, 715, 1941. (43.) Carrera, J. L.: Rev. Arg. de dermatosifil., 16, 391, 1932. (44.) Carter, B. B.: Am. J. Syph., Gon. and Ven. Dis., 26, 629, 1942. (45.) Chana, C. P.: Rev. méd. de Chile, 69, 715, 1941. (46.) Chargin, L., and Rein, C. R.: Arch. Dermat. and Syph., 44, 1031, 1941. (47.) Chung, H. L., and Chang, F. C.: Chinese Med. J., 55, 6, 1939. (48.) Clifton, W. M., and Heinz, M. O.: J. Am. Med. Assn., 114, 1731, 1940. (49.) Coburn, A. F., and Moore, D. H.: Bull. Johns Hopkins Hosp., 73, 196, 1943. (50.) Corrigan, M.: J. Infect. Dis., 41, 457, 1927. (51.) Coutts, W. E., Bustamente, B., and Gho, J.: Rev. chilena de hig. y med. prev., 4, 37, 1944. (52.) Craig, C. F.: J. Am. Med. Assn., 62, 1232, 1914. (53.) Craig, C. F., and Nichols, H. J.: J. Exp. Med., 16, 336, 1912. (54.) Crawford, G. M., and Ray, L. F.: J. Am. Med. Assn., 113, 1715, 1939. (55.) Cumming, H. S., Hazen, H. H., Sanford, A. H., Senear, F. E., Simpson, W. M., and Vonderlehr, R. A.: J. Am. Med. Assn., 104, 2083, 1935. (56.) Curth, W.: Am. J. Syph., 17, 164, 1933.  
 (57.) Davis, B. D.: Medicine, 23, 359, 1944. (58.) Davis and Co-workers: Cited by Davis, 1944. (59.) Davis, D., and Sidel, N.: Boston Med. and Surg. J., 197, 1516, 1928. (60.) Dawber, T. R.: Ann. Int. Med., 19, 651, 1943. (61.) Dawson, M. H., and Hobby, G. L.: Trans. Assn. Am. Phys., 54, 329, 1939. (62.) De Gregorio: Cited by May, 1940. (63.) De Groat, A.: J. Lab. and Clin. Med., 28, 882, 1943. (64.) Depetris, P.: Rev. Assn. Med. Argent., 50, 1092, 1936. (65.) Desneux, J.: J. belge neurol. et de psychiat., 35, 726, 1935. (66.) Drew, W. R. M., Samuel, E., and Ball, M.: Lancet, i, 761, 1943. (67.) Dudumi and Saratzeano: Cited by Gougerot and Burnier. (68.) Dujardin, B.: Ann. de mal. vén., 79, 129, 1920. (69.) Dulaney, A. D.: Am. Rev. Tuberc., 6, 192, 1922. (70.) Dünner, L., and Mayer, R.: Med. Klin., 29, 773, 1933.  
 (71.) Eagle, H.: (a) J. Lab. and Clin. Med., 17, 778, 1932; (b) Ibid., 17, 778, 1932; (c) Ibid., 18, 821, 1933; (d) J. Immunol., 29, 467, 1935; (e) Laboratory Diagnosis of Syphilis, St. Louis, Mosby, 1937; (f) Am. J. Syph., Gon. and Ven. Dis., 25, 7, 1941; (g) Ibid., 26, 641, 1942. (72.) Eagle, H., and Hogan, R. B.: J. Exp. Med., 71, 215,

1940. (73.) Eagle, H., Hogan, R. B., Mohr, C. F., and Black, S. H.: *Am. J. Syph., Gon. and Ven. Dis.*, 25, 397, 1941. (74.) Eagle, H., Mays, J. R. S., Hogan, R. B., and Burney, L. E.: *Am. J. Syph., Gon. and Ven. Dis.*, 25, 401, 1941. (75.) Ehrich, W. E., and Harris, T. N.: *Science*, 101, 28, 1945. (76.) Eldh, S. M.: *Svenska Läkartidningen*, 29, 373, 1932. (77.) Eller, K.: *Ztschr. f. Immunitätsforsch. u. exp. Ther.*, 74, 397, 1932. (78.) Erickson, P. T., and Eagle, H.: *Ven. Dis. Inf.*, 21, 31, 1940. (79.) Ester, F.: *Gior. di batteriol. e immunol.*, 17, 502, 1936.
- (80.) Faget, G. H., and Ross, H.: *Ven. Dis. Inf.*, 25, 33, 1944. (81.) Fanconi, G.: *Schweiz. med. Wehnschr.*, 66, 821, 1936. (82.) Favorite, G. O.: (a) *Proc. Soc. Exp. Biol. and Med.*, 52, 297, 1943; (b) *Am. J. Med. Sci.*, 208, 216, 1944. (83.) Fellows, F. S., and Perry, W. B.: *Ven. Dis. Inf.*, 22, 237, 1941. (84.) Fischer, O., and Günsberger, O. D.: *Ztschr. f. Immunitätsforsch.*, 78, 295, 1933. (85.) Fitzgerald, E. M., Shepherd, M., and Kemp, J. E.: *Proc. Soc. Exp. Biol. and Med.*, 42, 427, 1939. (86.) Foord, A. G., and Bauckus, M.: *J. Lab. and Clin. Med.*, 13, 270, 1927. (87.) Forssman, J.: *Acta Soc. Med. Fenn. Duodecim.*, Ser. A, 15, 3, 1932. (88.) Fowler, W. M., and Tidrick, R. T.: *Am. J. Clin. Path.*, 10, 548, 1940. (89.) Fox, H.: *Am. J. Med. Sci.*, 139, 725, 1910. (90.) Frazier, C. N., and Hu, C. K.: *Proc. Soc. Exp. Biol. and Med.*, 30, 898, 1933. (91.) Frei, W.: (a) *Klin. Wehnschr.*, 8, 2134, 1929; (b) *J. Am. Med. Assn.*, 110, 1653, 1938. (92.) Freudenthal, W.: *Deutsch. med. Wehnschr.*, 56, 2216, 1930. (93.) Freund, J.: *J. Exp. Med.*, 51, 889, 1930.
- (94.) Gaeltgens, W., and Otto, A.: *Med. Klin.*, 25, 873, 1929; (b) *Ibid.*, 25, 390, 1929; (c) *Ztschr. f. Immunitätsforsch.*, 63, 398, 1929; (d) *Urol. and Cutan. Rev.*, 34, 165, 1930; (e) *Arch. Dermat. u. Syph.*, 176, 42, 1937-38. (95.) Gay Prieto: Cited by May, 1940. (96.) Gigante, D.: *Klin. Wehnschr.*, 20, 123, 1941. (97.) Gooding, S. E. F.: *Practitioner*, 127, 468, 1931. (98.) Gougerot, H., and Burnier, R.: *V Congrès des Dermatologistes et Syphiligraphes de Langue fran.*, Lyon, Rapports, p. 55, 1934. (99.) Graña, A., and Torres, L. A.: *Arch. Urug. de méd. cir. y especialid.*, 22, 202, 1943. (100.) Green, M. N., and Forster, G. F.: *Am. J. Syph., Gon. and Ven. Dis.*, 25, 632, 1941. (101.) Greenbaum, S. S., and Yagle, E.: *J. Am. Med. Assn.*, 87, 318, 1926. (102.) Greene, R. A., and Brezeale, B. S. A.: *J. Lab. and Clin. Med.*, 25, 104, 1939. (103.) Greene, R. A., Brezeale, E. L., and Andes, J. E.: *Southwest. Med.*, 25, 46, 1941. (104.) Greene, R. A., and Harding, H. B.: *Am. J. Syph., Gon. and Ven. Dis.*, 25, 89, 1941. (105.) Greene, R. A., Harding, H. B., Hudspeth, W. T., and Pistor, W. J.: *J. Lab. and Clin. Med.*, 23, 763, 1938. (106.) Greer, A. E.: *Texas State J. Med.*, 19, 485, 1924. (107.) Greval, S. D. S.: *Indian J. Ven. Dis. and Dermat.*, 9, 63, 1943. (108.) Greval, S. D. S., Sen Gupta, P. C., and Napier, L. E.: *Indian J. Med. Res.*, 27, 181, 1939. (109.) Grumbach, A.: *Helvet. med. acta*, 7, 528, 1941. (110.) Gunn, W.: *Brit. Med. J.*, 1, 183, 1932. (111.) Gutman, A. B., and Williams, R. D.: *J. Clin. Invest.*, 15, 458, 1936. (112.) Gutman, A. B., and Wise, C. R.: *Proc. Soc. Exp. Biol. and Med.*, 35, 124, 1936.
- (113.) Halecrow, J. P. A., Owen, L. M., and Rodger, N. O.: *Brit. Med. J.*, 2, 443, 1943. (114.) Haller, D. A.: *J. Am. Med. Assn.*, 66, 882, 1916. (115.) Harris, A., and Portnoy, J.: *Ven. Dis. Inf.*, 25, 353, 1944. (116.) Harrison, L. W., and Osmond, T. E.: *Brit. J. Ven. Dis.*, 19, 108, 1943. (117.) Hatz, B.: *Am. J. Clin. Path.*, 8, 39, 1938. (118.) Hazen, H. H.: *Arch. Dermat. and Syph.*, 37, 431, 1938. (119.) Hazen, H. H., and others: *Ven. Dis. Inf.*, 17, 253, 1936; also *Internat. J. Leprosy*, 4, 315, 1936. (120.) Hazen, H. H., Senear, F. E., Parran, T., Sanford, A. H., Simpson, W. M., and Vonderlehr, R. A.: *Arch. Dermat. and Syph.*, 37, 431, 1938. (121.) Hecht, H.: *Prag. med. Wehnschr.*, 39, 316, 1914. (122.) Hegglin, R., and Grumbach: *Schweiz. med. Wehnschr.*, 71, 578, 1941. (123.) Heimoff, L. L.: *Mil. Surg.*, 95, 419, 1944. (124.) Heinemann, H.: *München. med. Wehnschr.*, 68, 1551, 1921. (125.) Hellerström: Cited by May, 1940. (126.) Hentschel, H., and Szego, L.: *Klin. Wehnschr.*, 8, 1395, 1929. (127.) Hill, A.: *J. Pediat.*, 21, 207, 1942. (128.) Hinrichsen, J.: *Ven. Dis. Inf.*, Suppl. 14, 1941. (129.) Holmberg, C. G., and Grönwall, A.: *Ztschr. f. physiol. Chem.*, 273, 199, 1942. (130.) Hopkins, R., and Faget, G. H.: *J. Am. Med. Assn.*, 126, 937, 1944. (131.) Horowitz, H. L.: *Illinois Med. J.*, 52, 146, 1927. (132.) Hoverson, E. T., Petersen, W. F., and Sackett, DeL.: *J. Lab. and Clin. Med.*, 20, 337, 1935. (133.) Howard, M. E., Eisenman, A. J., and Strauss, M. J.: *Am. J. Syph., Gon. and Ven. Dis.*, 23, 83, 1939. (134.) Hudson, E. H.: *Am. J. Syph., Gon. and Ven. Dis.*, 21, 45, 1937.
- (135.) Ingraham, N. R., Jr., and Mayer, V. R.: *Am. J. Syph., Gon. and Ven. Dis.*, 24, 23, 1940. (136.) Isaacs, H. J.: *Illinois Med. J.*, 71, 161, 1937. (137.) Ishibashi, T.: *Tohoku J. Exp. Med.*, 30, 287, 1937.
- (138.) Jacobsthal, E.: *Bol. Sanit. de Guatemala*, 12, 190, 1941. (139.) Jahnel, F.: *Klin. Wehnschr.*, 20, 1089, 1941. (140.) Jeghers, H., and Selesnick, S.: *Internat. Clin.*, 3, 248, 1937. (141.) Jersild, M.: *Acta dermat-venereol.*, 18, 491, 1937. (142.) Johnsrud, R. L.: *U. S. Nav. Med. Bull.*, 39, 277, 1941. (143.) Jones, C. A., and Rome, H. P.: *Am. J. Clin. Path.*, 9, 421, 1939.

- (144.) Kabat, E. A. D., Moore, D. H., and Landow, H.: *J. Clin. Invest.*, 21, 571, 1942. (145.) Kagan, B. M.: *AM. J. MED. SCI.*, 206, 309, 1943. (146.) Kahn, R. L.: (a) *Arch. Dermat. and Syph.*, 39, 92, 1939; (b) *Ibid.*, 41, 517, 1940; (c) *Univ. Hosp. Bull. (Michigan)*, 6, 26, 1940; (d) *Ibid.*, 8, 45, 1942; (e) *Serology in Syphilis Control*, Baltimore, Williams & Wilkins, 1942; (f) *J. Lab. and Clin. Med.*, 28, 1175, 1943. (147.) Kahn, R. L., Marcus, J., McDermott, E. B., and Adler, J.: *J. Invest. Dermat.*, 5, 459, 1942. (148.) Kahn, R. L., McDermott, E. B., and Adler, J.: *Proc. Soc. Am. Bact., J. Bact.*, 45, 73, 1943. (149.) Kahn, R. L., McDermott, E. B., and Marcus, S.: *Am. J. Syph., Gon. and Ven. Dis.*, 25, 151, 157, 162, 173, 1941. (150.) Kampmeier, R. H.: *J. Lab. and Clin. Med.*, 20, 531, 1935. (151.) Kampmeier, R. H., Smith, D. W., and Larsen, R. M.: *AM. J. MED. SCI.*, 198, 516, 1939. (152.) Kandler, H.: *Arch. Dermat. u. Syph.*, 181, 315, 1940. (153.) Kast, C. C., and Kolmer, J. A.: *Am. J. Syph., Gon. and Ven. Dis.*, 27, 309, 1943. (154.) Kaufman, R. E.: *J. Lab. and Clin. Med.*, 26, 1439, 1941. (155.) Kelley, M. F., and Short, J. J.: *J. Lab. and Clin. Med.*, 21, 910, 1936. (156.) Kelson, S. R., and White, P. D.: *Ann. Int. Med.*, 22, 40, 1945. (157.) Kemp, J. E., Fitzgerald, E. M., and Shepherd, M.: *Am. J. Syph., Gon. and Ven. Dis.*, 24, 537, 1940. (158.) Kilduffe, R. A., and Hersohn, W. W.: *Am. Rev. Tuberc.*, 19, 228, 1929. (159.) Kissmeyer, A.: *Ugesk. f. Læger*, 99, 213, 1937. (160.) Kitchen, S. F., Webb, E. L., and Kupper, W. H.: *J. Am. Med. Assn.*, 112 1443, 1939. (161.) Kline, B. S.: (a) *Am. J. Clin. Path.*, 12, 48, 1942; (b) *Ohio State Med. J.*, 39, 439, 1943. (162.) Kneeland, Y., and Smetana, H. F.: *Bull. Johns Hopkins Hosp.*, 67, 229, 1940. (163.) Knott, L. W., Bernstein, L. H. T., Eagle, H., Billings, T. E., Zobel, R. L., and Clark, E. G.: *Am. J. Syph., Gon. and Ven. Dis.*, 27, 657, 1943. (164.) Kogoj, Fr.: *Bull. Soc. franç. dermat. et syph.*, 49, 1064, 1939. (165.) Kolmer, J. A.: (a) *Serum Diagnosis by Complement Fixation*, Philadelphia, Lea & Febiger, 1928; (b) *Am. J. Syph.*, 13, 248, 1929; (c) *J. Am. Med. Assn.*, 93, 1429, 1929; (d) *Proc. Soc. Exp. Biol. and Med.*, 42, 183, 1939; (e) *Am. J. Clin. Path.*, 11, 402, 1941; (f) *Ibid.*, 12, 480, 1942; (g) *Arch. Dermat. and Syph.*, 45, 455, 1942; (h) *Am. J. Med. Technol.*, 9, 38, 1943; (i) *Am. J. Pub. Health*, 34, 510, 1944. (166.) Kolmer, J. A., and Denney, O. E.: *Arch. Dermat. and Syph.*, 8, 63, 1923. (167.) Kolmer, J. A., Ginsburg, I. W., and Lynch, E. R.: *Am. J. Clin. Path.*, 12, 316, 1942. (168.) Kolmer and Kast: Cited by Kolmer, J. A., *Am. J. Med. Tech.*, 9, 38, 1943. (169.) Kolmer, J. A., Kast, C. C., and Lynch, E. R.: (a) *Am. J. Syph., Gon. and Ven. Dis.*, 25, 300, 412, 1941; (b) *Ibid.*, 26, 142, 1942. (170.) Kolmer, J. A., and Lynch, E. R.: *Am. J. Clin. Path.*, 9, 136, 1939. (171.) Kolmer, J. A., Rule, A. M., and Trist, M. E.: *Am. J. Syph.*, 4, 641, 1920. (172.) Kolmer, J. A., Williams, W. W., and Laubaugh, E. E.: *J. Med. Res.*, 28, 345, 1913. (173.) Krag, P.: *Ugesk. f. Læger*, 98, 855, 1936. (174.) Krag, P., and Lönberg, A.: (a) *Acta dermat.-venereol.*, 19, 612, 1938; (b) *Ugesk. f. Læger*, 100, 497, 1938. (175.) Kroß, H., Schultze, F. D., and Zander, I.: *Klin. Wehnschr.*, 8, 783, 1929. (176.) Kuske, H.: *Dermat. Ztschr.*, 78, 137, 1938. (177.) Kutzell, W. C., and Puccinelli, V.: Cited in *Bull. U. S. Army Med. Dept.*, No. 80, p. 3, 1944. (178.) Landau, A.: *Acta Paediat.*, 26, 235, 1939. (179.) Landsteiner, K., *et al.*: (a) *Wien. klin. Wehnschr.*, 20, 1421, 1907; (b) *Proc. Soc. Exp. Biol. and Med.*, 23, 641, 1926; (c) *J. Exp. Med.*, 45, 45, 1927. (180.) Lane, J. F.: *Hosp. News (USPHS)*, 6, 19, 1939. (181.) Levit, L.: *Rev. méd. de Rosario*, 32, 96, 1942. (182.) Lindau, A.: *Acta chir. Scand.*, 82, 355, 1939. (183.) Lloyd, R. B.: *Indian Med. Gaz.*, 67, 1, 1930. (184.) Lloyd, R. B., and Mitra, G. C.: *Indian J. Med. Res.*, 14, 135, 1926. (185.) Lloyd, R. B., Muir, E., and Mitra, G. C.: (a) *Indian J. Med. Res.*, 12, 213, 1924; (b) *Ibid.*, 14, 667, 1927. (186.) Lloyd, R. B., Napier, L. E., and Mitra, G. C.: *Indian J. Med. Res.*, 17, 957, 1930. (187.) Lohe, H., and Rosenfeld, H.: *Dermat. Ztschr.*, 53, 373, 1928. (188.) Loveman, A. B.: *Bull. U. S. Army Med. Dept.*, No. 80, p. 95, 1944. (189.) Loveman, A. B., and Stocking, L.: *Arch. Dermat. and Syph.*, 29, 653, 1934. (190.) Lubitz, J. M.: (a) *Am. J. Clin. Path.*, 13, 139, 1943; (b) *Proc. Inst. Med. Chicago*, 14, 343, 1943. (191.) Lund, H.: *Am. J. Syph., Gon. and Ven. Dis.*, 26, 1, 1942. (192.) Lynch, F. W.: *Minnesota Med.*, 24, 843, 1941. (193.) Lynch, F. W., Boynton, R. E., and Kimball, A. C.: *J. Am. Med. Assn.*, 117, 591, 1941. (194.) Mackie, T. J., and Anderson, C. G.: *J. Path. and Bact.*, 44, 603, 1937. (195.) Malloy, A. M., and Kahn, R. L.: *J. Infect. Dis.*, 48, 243, 1941. (196.) Maltaner, E.: *Am. J. Trop. Med.*, 21, 145, 1941. (197.) Margarot, J., Rimbaud, P., and Ravoire, J.: *Bull. Soc. franç. dermat. et syph.*, 49, 1003, 1939. (198.) Matsumura, S.: *Tohoku J. Exp. Med.*, 23, 268, 1934. (199.) May, J.: (a) 1925, cited by May, 1940; (b) 1933, cited by May, 1940; (c) *Revist. Uruguay in Dermat. y Sif., Poradeno infitis*, vol. V, fascículo unico, 1940. (200.) McLean, A. J., and Munger, I. C., Jr.: *West. J. Surg.*, 46, 455, 1938. (201.) Meier, G.: *Klin. Wehnschr.*, 36, 845, 1920. (202.) Meirrowsky: *Deutsch. med. Wehnschr.*, 27, 1287, 1912. (203.) Menk, W.: *United Fruit Co. Med. Dept. Ann. Rep.*, 1926. (204.) Mills, J. H., and Jahn, E.: *J. Lab. and Clin. Med.*, 24, 1076, 1938-39. (205.) Mitchel, R. H., and Zetzel, L.: *War Med.*, 5, 356, 1944. (206.) Mohr, C. F., Moore, J. E., and Eagle, H.: *Arch. Int. Med.*, 68, 898, 1161, 1941.

- (207.) Mohr, C. F., Scott, V., Hahn, R. D., Clark, E. G., and Moore, J. E.: *Arch. Int. Med.*, 74, 390, 1944. (208.) Mohr, C. F., and Smith, C. A.: *Am. J. Syph., Gon. and Ven. Dis.*, 24, 322, 1940. (209.) Monticelli, M.: *Boll. d. Ist. sieroterap. milanese*, 11, 584, 1932. (210.) Moore, J. E.: (a) *Bull. Genitoinfectious Diseases*, 3, 1, 1940; (b) *The Modern Treatment of Syphilis*, 2nd ed., Springfield, Ill., Thomas, 1941. (211.) Moore, J. E., Eagle, H., and Mohr, C. F.: *J. Am. Med. Assn.*, 115, 1602, 1940. (212.) Morales Otero, P.: (a) *Porto Rico Health Rev.*, 2, 11, 1926; (b) *Porto Rico J. Puh. Health and Trop. Med.*, 7, 69, 1931. (213.) Morsch, J. R.: *Ugeskr. f. Læger*, 97, 392, 1935. (214.) Morgan, I. M., Schlesinger, R. W., and Olitsky, P. K.: *J. Exp. Med.*, 76, 357, 1942. (215.) Muir, E., and Roy, T. N.: *Leprosy Rev.*, 9, 13, 1938. (216.) Munch-Anderson, M.: *Hospitaltid*, 75, 1241, 1932. (217.) Murrell, T. W.: *Arch. Dermat. and Syph.*, 39, 667, 1939. (218.) Myers, R. M., and Perry, C. A.: *Am. J. Syph., Gon. and Ven. Dis.*, 26, 494, 1942. (219.) Myerson, M. C.: *J. Am. Med. Assn.*, 117, 1877, 1941.
- (220.) Nagell, H.: *Dermat. Wehnschr.*, 90, 795, 823, 1930. (221.) Nagell, H., and Langhans, J.: *Med. Klin.*, 24, 368, 1928. (222.) Needles, R. J.: *Arch. Neurol. and Psychiat.*, 34, 618, 1935. (223.) Neurath, H., *et al.*: *Science*, 101, 68, 1945. (224.) Nicolau, S., and Banciu, A.: *Compt. rend. Soc. de biol.*, 91, 1352, 1924. (225.) Noguchi, H.: *J. Am. Med. Assn.*, 58, 1163, 1912.
- (226.) Oberdoerffer, M. J.: *Dermat. Wehnschr.*, 111, 794, 1940. (227.) Oppenheim: Cited by Sézary and Terrasse. (228.) Owen, M., Brooks, B., and Tucker, LaM.: *Texas State J. Med.*, 38, 714, 1943.
- (229.) Pai, S. E.: *Chinese Med. J.*, 52, 595, 1937. (230.) Pangborn, M. C.: (a) *Proc. Soc. Exp. Biol. and Med.*, 48, 484, 1941; (b) *J. Biol. Chem.*, 143, 247, 1942. (231.) Parkes-Weber, F.: *Med. Press and Circ.*, 130, 65, 1930. (232.) Parkes-Weber, F., and Bode, O. B.: *München. med. Wehnschr.*, 78, 1598, 1931. (233.) Parran, T., and Emerson, K.: *Ven. Dis. Inf.*, 20, 1, 1939. (234.) Parran, T., Hazen, H. H., Mahoney, J. F., Sanford, A. H., Senear, F. E., Simpson, W. M., and Vonderlehr, R. A.: (a) *J. Am. Med. Assn.*, 109, 425, 1937, and *Ven. Dis. Inf.*, 18, 273, 1937; (b) *J. Am. Med. Assn.*, 117, 1167, 1941; (c) *Ven. Dis. Inf.*, 23, 355, 1942; (d) *Ibid.*, 23, 161, 1942.
- (235.) Parran, T., Hazen, H. H., Sanford, A. H., Senear, F. E., Simpson, W. M., and Vonderlehr, R. A.: *Am. J. Clin. Path.*, 7, 20, 1937; *Am. J. Pub. Health*, 27, 15, 1937; *Ven. Dis. Inf.*, 18, 4, 1937. (236.) Patrick, D. W., and Wolfe, D. M.: *U. S. Pub. Health Rep.*, 56, 1757, 1941. (237.) Pautrier, L. M.: (a) *Bull. Soc. franç. dermat. et syph.*, 49, 966, 1939; (b) *Nouvelle Pratique Dermatologique*, Paris, Masson, 1936. (238.) Pessano, J.: *Rev. Arg. de dermatosif.*, 16, 158, 1932. (239.) Pierce, L. F., and Brezeale, E. L.: *J. Invest. Dermat.*, 5, 249, 1942. (240.) Pockels, W.: *Klin. Wehnschr.*, 12, 431, 1933. (241.) Priest, R.: *J. Roy. Army Med. Corps*, 65, 159, 1935. (242.) Prochazka, K.: *Ciska Dermat.*, 10, 162, 1929.
- (243.) Radford, M., and Rolleston, J. D.: *Lancet*, ii, 18, 1930. (244.) Ratcliffe, A. W.: *J. Lab. and Clin. Med.*, 27, 729, 1942. (245.) Ravaut, P.: Cited by May. (246.) Ravaut, P., Boulin and Rabreau: 1924, cited by May, 1940. (247.) Rein, C. R., and Callender, G. R.: *Bull. U. S. Army Med. Dept.* No. 85, 108, 1945. (248.) Rein, C. R., and Elsberg, E. S.: *Am. J. Clin. Path.*, 14, 461, 1944. (249.) Rein, C. R., and Frank, S. B.: *Urol. and Cutan. Rev.*, 44, No. 9, 1940. (250.) Reisner, D.: *Am. Rev. Tuberc.*, 39, 289, 1944; *Ibid.*, 40, 437, 1944. (251.) Reynes, V., and Richard, J.: *Bull. Soc. path. exot.*, 33, 363, 1940. (252.) Robin, G.: *Compt. rend. Soc. de biol.*, 124, 865, 1937. (253.) Rominger, E., and Szego, L.: *Arch. f. Kinderheilk.*, 95, 255, 1932. (254.) Rosen, I., Rosenfeld, H., Bloom, D., and Krasnow, F.: *Arch. Dermat. and Syph.*, 39, 211, 1939. (255.) Rosenberg, A. A.: *Bull. U. S. Army Med. Dept.*, 84, 74, 1945. (256.) Rothbart, H. B.: *J. Pediatr.*, 11, 484, 1937. (257.) Ruge, H.: *Dermat. Wehnschr.*, 1930, cited by May, 1940. (258.) Rytz, F.: (a) *Proc. Soc. Exp. Biol. and Med.*, 32, 1501, 1935; (b) *Minnesota Med.*, 24, 321, 1941; (c) *Am. J. Clin. Path.*, 12, 166, 1942.
- (259.) Sachs, H.: *Brit. J. Ven. Dis.*, 18, 96, 1942. (260.) Sachs, H., Klopstock, A., and Weil, A. J.: *Deutsch. med. Wehnschr.*, 51, 589, 1925. (261.) Sadusk, J. F., Jr.: *J. Am. Med. Assn.*, 112, 1682, 1939; *Internat. Clin.*, 1, n.s. 4, 239, 1941. (262.) Salminen, Y. W.: *Finska läk-sällsk. handl. Helsingfors*, 70, 985, 1928. (263.) Saphir, W.: *Am. J. Clin. Path.*, 9, 306, 1939. (264.) Saunders, G. M., and Turner, T. B.: *South. Med. J.*, 28, 542, 1935. (265.) Schamberg, I. L.: *AM. J. MED. SCI.*, 201, 67, 1941. (266.) Schaumann and Heden: Cited by Gougerot and Burnier. (267.) Schönfeld: Cited by Gougerot and Burnier. (268.) Schreus, H. T., and Foerster, R.: *Ztschr. f. Immunitätsforsch. u. exp. Ther.*, 82, 53, 1934; *Ibid.*, 82, 59, 1934. (269.) Scott, V., Reynolds, F. W., and Mohr, C. F.: *Am. J. Syph., Gon. and Ven. Dis.*, 28, 431, 1944. (270.) Sellek Azzi, A., and del Frade, A.: *Arch. d. med. inf.*, 10, 61, 1941. (271.) Sézary, A., and Terrasse, J.: *Ann. dermat. et syph.*, 6, 21, 1935. (272.) Sherwood, N. P., Bond, G. C., and Canuteson, R. I.: *Am. J. Syph., Gon. and Ven. Dis.*, 25, 179, 1941. (273.) Sherwood, N. P., Bond, G. C., and Clark, H. F.: *J. Bact.*, 38, 231, 1939. (274.) Sherwood, N. P., and Collins: *J. Bact.*, 44, 392, 1942. (275.) Simon, L.: *Bull.*



- Soc. path. exot., 18, 378, 1925. (276.) Smith, C. R.: J. Lab. and Clin. Med., 18, 396, 1932, 1933. (277.) Smith, W.: Lancet, 1, 754, 1937. (278.) Snow, C. G., and Cooper, A. T.: AM. J. MED. SCI., 152, 185, 1916. (279.) Solomon, P., Dailey, M. E., Fremont-Smith, F.: Arch. Neurol. and Psychiat., 31, 1222, 1934. (280.) Sompayrac, L., and Hailey, H. E.: Arch. Dermat. and Syph., 49, 355, 1944. (281.) Sorba, M.: Monatschr. f. Geburtsh. u. Gynäk., 109, 49, 73, 1939. (282.) Souders, C. R.: Lahey Clin. Bull., 3, 27, 1942. (283.) Soule, M. H.: Internat. J. Leprosy, 3, 181, 1935. (284.) Spiegel, R.: Monatschr. f. Geburtsh. u. Gynäk., 91, 340, 1932. (285.) Sprunt, T. P.: Internat. Clin., 3, 93, 1933. (286.) Stern, C.: München. med. Wehnschr., 79, 583, 1932. (287.) Stern, M.: Ztschr. f. Immunitätsforsch. u. exp. Ther., 5, 201, 1910. (288.) Sterzi, G., and Staudacher, V.: (a) Gior. ital. di dermat. e sif., 80, 777, 1939; (b) Abstr., Am. J. Syph., Gon. and Ven. Dis., 25, 387, 1941. (289.) Stokes, J. H.: (a) Modern Clinical Syphilology, 1st ed., Philadelphia, Saunders, 1926; (b) Ann. Int. Med., 2, 1139, 1929; (c) Modern Clinical Syphilology, 2nd ed., Philadelphia, Saunders, 1934; (d) Am. J. Syph., Gon. and Ven. Dis., 23, 549, 1939. (290.) Stokes, J. H., Beerman, H., and Ingraham, N. R., Jr.: Modern Clinical Syphilology, 3rd ed., Philadelphia, Saunders, 1944. (291.) Strickler, A., Munson, H. G., and Sidlick, D. M.: J. Am. Med. Assn., 75, 1488, 1920. (292.) Stryecki, T.: (a) Bull. internat. Acad. polon. d. sc. et d. lett. Cl. méd., 115, 128, 1938; (b) Abstr. Acta dermat.-venereol., 20, 168, 1939. (293.) Stuckey, G. C., and Huntley, W. B.: Am. Rev. Tuberc., 14, 724, 1926. (294.) Sulzberger, M. B.: Year Book of Dermatology and Syphilology, Chicago, Year Book Pub. Co., 1943. (295.) Sulzberger, M. B., and Wise, F.: J. Am. Med. Assn., 99, 1407, 1932. (296.) Sweany, H. C.: Trans. Nat. Tuberc. Assn., 37, 164, 1941. (297.) Taussig, A. E.: J. Lab. and Clin. Med., 29, 473, 1944. (298.) Taussig, A. E., and Orgel, M. N.: J. Lab. and Clin. Med., 22, 614, 1936-37. (299.) Taussig, A. E., and Somogyi, J. Lab. and Clin. Med., 25, 1070, 1940. (300.) Taylor, E. S., and Heiss, M. E.: J. Am. Med. Assn., 124, 1100, 1944. (301.) Thaysen, T. E. H.: Acta med. Scand., 55, 281, 1921. (302.) Thomas, G. E., and Garrity, R. W.: U. S. Naval Med. Bull., 39, 72, 1941; Ibid., 39, 272, 1941. (303.) Throne, B.: Arch. Dermat. and Syph., 12, 33, 1925. (304.) Ts'un, T., and Chung, H. L.: Chinese Med. J., Suppl., p. 315, 1938. (305.) Van den Branden, F.: J. Am. Med. Assn., 86, 1925, 1926. (306.) Vasek: Zentralbl. f. d. ges. Ophthalm., 5, 344, 1921. (307.) Vincent, C.: Rev. neurol., 23, 652, 1912. (308.) Vonderlehr, R. A., and Usilton, L. J.: J. Am. Med. Assn., 120, 1369, 1942. (309.) Waldenström, J.: Acta med. Scand., 91, 53, 1937. (310.) Walker, W. H.: Bull. U. S. Army Med. Dept., 83, 80, 1944. (311.) Warnecke, B.: J. Trop. Dis., 40, 689, 1943. (312.) Warren, E. W.: AM. J. MED. SCI., 201, 483, 1941. (313.) Warring, F. C., Jr.: Am. Rev. Tuberc., 40, 175, 1939. (314.) Wassermann, A. V.: Berl. klin. Wehnschr., 58, 9, 193, 1921. (315.) Wawersig, R.: Med. Klin., 33, 1737, 1937. (316.) Weil, A. J.: Bact. Rev., 5, 293, 1941. (317.) Werlin, S. J., Dolgopol, V. B., and Stern, M. E.: AM. J. MED. SCI., 201, 474, 1941. (318.) Wichels, P., Hürthle, R., and Maley: München. med. Wehnschr., 76, 1759, 1929. (319.) Wiener, A. S., and Derby, I. M.: (a) Arch. Dermat. and Syph., 39, 999, 1939; (b) Proc. Soc. Exp. Biol. and Med., 38, 487, 1938. (320.) Wile, U. J., and Snow, J. S.: J. Invest. Dermat., 4, 103, 1941. (321.) Williams, R. D., and Gutman, A. B.: Proc. Soc. Exp. Biol. and Med., 34, 91, 1936. (322.) Wilson, R., and Levin, S. L.: AM. J. MED. SCI., 191, 696, 1936. (323.) Windson-McLean, A. A.: J. Med. Australia, 1 (30th year), 520, 1943. (324.) Witebsky, E.: (a) Zentralbl. f. Bakt., 122, 70, 1931; (b) Ztschr. f. Immunitätsforsch., 80, 323, 1933; (c) Arch. Path., 26, 1083, 1938. (325.) Wooley, P. V.: J. Pediat., 8, 693, 1936. (326.) Wydrin, A.: Wien. Arch. f. inn. Med., 25, 231, 1934. (327.) Yagle, E. M., and Kolmer, J. A.: Arch. Dermat. and Syph., 6, 183, 1922. (328.) Zuger, B., and Moffat, G. B.: Ven. Dis. Inf., 25, 271, 1944.

## ADDENDUM

Since the foregoing material was prepared, the continuing interest in the subject of biologic false positive serologic reactions to the tests for syphilis is indicated by the appearance of new studies.

Elmes and Findlay (J. Roy. Army Medical Corps, 84, 29, 1945) studied the Kahn test in 80 British soldiers serving in a hyperendemic malaria zone and suffering from malignant tertian malaria, and found that 23 of them gave at some period a positive reaction. Only 1 of the patients gave evidence of syphilis. The authors call attention to the 1940 version of the Kahn verification test as a possible means of differentiating syphilis from malaria.

The influence of malaria on the cerebrospinal fluid Wassermann reaction as well as the incidence of biologic false positive reactions in the blood Kahn and Wasser-

mann tests was made the subject of a study by Potter, Bronstein and Gruber (J. Am. Med. Assn., 127, 699, 1945). They found in 100 consecutive male patients with naturally acquired malaria that none yielded positive reactions to the cerebrospinal fluid Wassermann test but 12% of the men had positive blood reactions and 10% had doubtful reactions. This indicated to the authors that the factors which produce the false results in the blood are not present in the cerebrospinal fluid. This study also emphasizes that a diagnosis of syphilis should not be made on the basis of a single test at any time. After an acute attack of malaria, at least 1 month should elapse before taking blood for further testing. In a rejoinder to this report, Brandt (J. Am. Med. Assn., 128, 152, 1945) calls attention to unpublished observations on patients inoculated with a strain of *Plasmodium vivax* acclimatized to transmission from man to man. Every case became seropositive after the sixth fever bout, but every case became seronegative again within 8 weeks after termination of malaria; the most sensitive test (Wassermann with R. Mueller's antigen) became positive sooner and stayed so longer than less sensitive ones. (Meinicke's earlier methods and the Sachs-Georgi reaction.) Because the Henry test (Arch. Inst. Prophylac., 1, 341, 1929) in inoculation malaria (Brandt, R., and Horn, L.: Klin. Wchnschr., 14, 1538, 1935) yields a curve of reactions from negative to positive, to negative, which closely resembles the curve of the non-specific reactions for syphilis, and as Henry describes the behavior of his test in malaria disease just the way Brandt and Horn found it in inoculation malaria, Brandt suggested that one may expect the same parallelism in the non-specific reactions, meaning that a certain time after cessation of fever attacks, malaria does not produce such reactions. A negative Henry test, therefore, by indicating that the period of manifest malaria infection has passed, would enhance the dependability of a positive serologic reaction to the tests for syphilis, where malaria has to be taken into account. From extensive studies of patients (former Austrian soldiers) with a history of malaria, there was no evidence to indicate that beyond the stage of attacks malaria has any influence on the outcome of the serologic syphilis reaction.

Rein and Elsberg (Am. J. Syph., Gon. and Ven. Dis., 29, 303, 1945) presented a detailed report on the effect of smallpox vaccination on the serologic reactions. They used a serologic battery: Kline diagnostic, Kline exclusion, flocculation tests, and the Kolmer complement fixation test. An attempt was made to do weekly tests on their patients (in some cases 8 to 12 days elapsed between the repeated examinations). The subjects received in addition to the smallpox vaccination, injections of tetanus toxoid and typhoid vaccine on the same day; a second dose of typhoid vaccine the following week; a third typhoid vaccination the 3rd week; a second dose of tetanus toxoid the 4th week; and a third dose of tetanus toxoid the 7th week. Of 129 individuals who developed a vaccinoïd or vaccinia reaction, 58 (44.9%) showed doubtful or positive serologic reactions to the tests for syphilis. Of this group, 50 (86.2%) developed their first positive serologic reaction between the 8th and 14th day following the vaccination. Of 80 individuals who developed vaccinia reactions, 41 (51.2%) showed false positive serologic reactions, whereas 49 individuals developed vaccinoïd reactions, of whom more than 17 (34.7%) showed false positive reactions. This indicates the possibility that false positive reactions occur more frequently in patients in the vaccinia group than in the vaccinoïd group. There was, however, no correlation between the incidence and titer of the false positive reactions and the severity of the skin reaction to the vaccine virus. In the immune reactor group, 36 patients (13%) developed doubtful serologic reactions to one or more tests. Revaccination of a small group (after 3 years) yielded no false positive serologic reactions. A group of 20 patients which was given only typhoid immunization, and another group of 16 patients receiving only tetanus toxoid injections, yielded no false positive reactions. This type of material merits continued investigation because of the serious medical and psychological import of positive serologic reactions in military personnel.

Hegglin (J. Am. Med. Assn., 129, 150, 1945), reemphasizes the problem of pneumonia with a positive Wassermann reaction.

In addition to the study of the incidence of false positive reactions to the tests for syphilis, modification of technique, new tests or evaluation of tests, designed to diagnose false reactions have continued to hold the attention of investigators.

Brown, Kolmer and Lynch (*Am. J. Syph., Gon. and Ven. Dis.*, 29, 200, 1945) have studied the effect of sodium hydroxide on biologic false positive and anti-complementary serologic reactions in syphilis. They found the addition of 0.1 cc. of N/3 or N/4 solutions of sodium hydroxide to 1 cc. of serum before heating at 55° C. has proved effective in preventing biologic false positive Kolmer, Kahn and Mazzini reactions in serum of normal rabbits, in presumably non-syphilitic individuals with malaria, infectious mononucleosis, and virus pneumonia. Less effective results were observed with the serums of presumably non-syphilitic epers. In contrast with the other diseases, N/4 sodium hydroxide yielded more effective results in leprosy than did N/3 sodium hydroxide. Addition of the alkali to syphilitic serums before heating results in the inactivation or destruction of some of the syphilitic reagin but false negative reactions are apt to occur in the Kolmer test only in the case of serums containing small amounts of reagin. The addition of N/3 or N/4 sodium hydroxide to rabbit and human serums has proved effective in the prevention of the anticomplementary reactions in the Kolmer complement fixation test.

Cooper (*J. Invest. Dermat.*, 6, 109, 1945; *Proc. Soc. Exp. Biol. and Med.*, 57, 248, 1944) made an electrophoretic study of syphilitic serums and attempted to identify the serum fraction carrying syphilitic reagin. He showed that there are characteristics and significant alterations in the serum proteins after infection in syphilis. There is an increase in all of the electrophoretic globulin fractions which occurs soon after infection and persists throughout the course of the disease in the absence of adequate treatment. In some cases of apparently false positive serums, the changes found in syphilis do not occur. The reagin for the Kahn and Wassermann reactions has been shown to occur in the  $\gamma$  globulin fraction. In the 1944 study, Cooper stated that the  $\beta$  or  $\gamma$  globulin fractions, or both, had been identified as carriers of the Wassermann and Kahn reagins.

Rein and Elsberg (*J. Invest. Dermat.*, 6, 113, 1945) ask whether the current verification tests are of practical value in the serodiagnosis of syphilis. After an exhaustive and careful analysis of the confirmation or verification tests and the addition of an unpublished, original method (Rein-Pillemer), they conclude that none of the methods presented has been able to distinguish consistently between true and false positive serologic reactions. There is an urgent need for a procedure which will perform this differential function and the authors suggest that any new procedure should be subjected to critical evaluation by a selected committee of serologists and clinicians before it is proposed to and by the medical profession at large.

---

## OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF  
NOAH D. FABRICANT, M.D.

ASSISTANT PROFESSOR, DEPT. OF LARYNGOLOGY, RHINOLOGY AND OTOTOLOGY, UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE, CHICAGO, ILL.

---

## CANCER OF THE MOUTH: ITS PRESENT DAY TREATMENT

BY WALTER MAYNE, M.D.

ATTENDING PLASTIC AND ORAL SURGEON, COOK COUNTY HOSPITAL, AND INSTRUCTOR IN PLASTIC AND ORAL SURGERY, UNIVERSITY OF ILLINOIS DENTAL SCHOOL, CHICAGO, ILL.

Of the cancer deaths in the United States 3% are malignant tumors of the mouth.

Studies of the statistics of men who have had a wide experience in oral cancer and who have not been biased in their opinion as to the use of either radiation or surgery show a high incidence in 5 year "cures" in mouth cancer—the percentage of cures ranking only below skin and breast cancer, in the hands of these individuals. However, patients with mouth cancers

are unfortunately taken care of for sometime by physicians who are relatively inexperienced in the complexities of oral cancer and are too conservative in radiation therapy or surgery.

The most common precancerous lesion of the mouth is leukoplakia. In an individual with leukoplakia, all of the oral mucosa undergoes a change, but the localized area of leukoplakia is the most marked. The transition to malignancy is marked by chronic fissure, ulceration, a reddish elevated papule, or hardness of the tissues surrounding the leukoplakia. Papillomas of the mouth may turn malignant as may spots of oral mucosa that are constantly subject to trauma in individuals with ill-fitting dentures or rough tooth surfaces.

Epitheliomas of the cheek are usually of the squamous-cell type, and grossly appear red and fleshy; the patient can sometimes give a history of carrying a tobacco quid or betel nut quid at the site of the malignancy. Extensive lesions of the buccal mucosa are common in mouth cancer. These areas spread to either alveolus, hard palate or involve the angle of the mouth; occasionally the cheek is perforated. When seen by a competent therapist these malignant areas average 4 cm. in width.<sup>11</sup>

At this stage carcinomas are often ulcerative, burrowing and exposing bone while the papillary types are cauliflower-like.

"In general, it may be said that the growths of the cheek are fairly sensitive to radium, except when they are very superficial and of the leukoplakic type. The softer and more fleshy the growth, the more successful is radium likely to be."<sup>15</sup>

When the growth is of the hard indurative type, diathermy excision of the lesion seems to be the treatment of choice.<sup>1,8,15</sup>

However, it is good practice to embed radium at the periphery of the excised area at the time of operation. The Ontario, Canada, Cancer Centers treated 103 cases of buccal mucosa from 1934 to 1939, almost exclusively with Roentgen ray and radium, with a survival rate of 50%.<sup>14</sup>

If one wishes to attempt the control of a fungating malignant mass with radium alone, the bulk of the lesion may be easily reduced with a diathermy knife and thus permit the radium to be distributed more judiciously and economically. In lesions which are radiosensitive more reliance should be placed in radium than surgery.

"Epitheliomas of the cheek have a marked tendency to involve the cervical lymph nodes; and even though none of the regional nodes are palpably enlarged, this does not rule out the possibility of their being involved. Consequently, unless the local lesion is very small and very low grade, we believe a block dissection of the cervical lymph nodes is indicated whether or not the lymph nodes are involved clinically."<sup>16</sup> Where the primary has reached the alveolar process it is advisable to destroy the underlying bone by cauterization at the time of the combined excision and neck dissection.<sup>1</sup> Jorstad prefers not to do a routine neck dissection and awaits palpable nodes. On those cases which have freely movable nodes, and on which he did perform a submaxillary neck dissection, 66% were found to possess cancerous nodes—an important fact for those to be conscious of who are inclined to wait and hope that these freely movable nodes will turn out to be merely inflammatory glands. In 116 cases involving a buccal mucosa, alveolar process, palate and velum that were treated by excision alone, either with the knife or cautery, a 5 year survival rate of 34% was obtained. In those receiving a unilateral neck dissection in addition to care of the primary, the survival rate was raised to 53%.<sup>8</sup>

If radium treatment is decided upon, the physician should be conscious

of some general principles. "Radium implantation is greatly facilitated by a good general anesthetic, as a poor anesthetic renders accurate implantation difficult. Intratracheal anesthesia is the most suitable type with the tube passed through the nose leaving the mouth available to the therapist.<sup>13</sup> Postoperatively, the usual routine for prevention of bronchopneumonia should be instituted. The needles after implantation should have the eye end stitched into the adjacent tissue, thus preventing their loosening and dislodgment. The radium silks leading from the mouth may be kept fairly clean by passing them through a flexible rubber tube. If different strength needles are used, or if some are to be taken out sooner than others, silk threads of various colors should be used. An assortment of mouth gags for working in various areas of the mouth are necessary, but most important is a good light.

"The simplest type of radium needle implantation used in the mouth is the 'single plane implantation.' In this the area to be treated—about 1 cm. clear of the known lesion in every direction—is outlined with radium needles of normal linear intensity in some rectangular form. The center is then put in parallel lines of needles of one-half the normal linear intensity about 1 cm. apart, in accordance with Paterson-Parker dosage system. The dose to be given is calculated at 0.5 cm. from the plane. Thus a block of tissue the size of the plane and 1 cm. thick is irradiated to a select dosage."<sup>13</sup>

"Unless the plane has a very large area, it is wise to give a higher dosage when a single plane implantation is used, than would be the case where a bigger volume is being treated by a multiplane or volume technique." The effective range of this type of implantation is small, and it is not always possible to be sure of the extent of the lesion. As a rough working rule, it is both safe and wise to give doses of the order of 7000 r. in 7 to 10 days from medium-sized planes, and 7500 r. from small planes. A medium-sized implantation should only be given doses in the region of 6000 to 6500 r. in a similar period. Single plane implantation of larger areas, for example, the whole cheek, only tolerate smaller doses in the neighborhood of 6000 to 6500 r."<sup>13</sup>

If the single plane technique is to be used in the cheek it will be found much easier to insert the needles through the cheek rather than to attempt the corners of the mouth, because of their rotundity. The curvature of the cheek also makes vertical insertion more feasible than horizontal insertion. The 3 mg. needles of 4.5 cm. active length may be inserted upwards with a finger in the mouth steadying the cheek. Occasionally parotitis from perforation of the parotid duct is a sequela.<sup>13</sup>

A sandwich mold can also be used for cheek lesions near the mouth angles. Both parts of the mold are made of dental compound with the needles embedded in it. The radium mucosa distance of the intra-oral plane is 0.5 cm., while the radium skin distance is 1 cm. A winged nut holds the plates together, and a projection of the mold serves as a bite block to hold the mold in position. Where the malignancy of the cheek is near the bone of either jaw, a sequestrum may later form due to the death of the superficial plate of the jaw.<sup>15</sup>

"The prognosis of radium treated carcinomata of the cheek is good, so long as radiation is sufficient. A small burn is not of serious import, and can be treated later by diathermy. Under radiation, on the other hand, is certain to be followed by recurrence, and the recurrence may be resistant to radium treatment."<sup>15</sup> Martin has reported 40% of his cheek cases controlled after 2½ years treated exclusively by radium.<sup>12</sup>

After several weeks following radiation there should be present a superficial ulcer of a wash-leather appearance covering the area larger than the original growth.

Again, in the malignancy of the tongue and floor of the mouth, the squamous cell epitheliomas far outnumber the occasional lymphosarcoma, adenocarcinomas and endotheliomas. These epidermoid carcinomas are usually found at the lateral border of the tongue, but sometimes are seen on the undersurface and spreading out involving the mouth floor. The cancers on the dorsum are often at the site of an old luetic scar. The tongue lesions usually are seen as ulcers with ragged edges "woody" to the touch, and hard at the base. The rubbery-like feel of fibrous scar tissue is absent here. Necrosis is present in the larger lesions, and this necrotic area is soft.<sup>8</sup> Tuberculosis, syphilis, fibromas, cysts, actinomycosis, blastomycosis and the angiomas must be borne in mind when a papillary form of tongue cancer is considered.

The trend in therapy in dealing with the floor of the mouth and tongue carcinomas is definitely veering toward radiation rather than surgery. However, Erich believes that "the larger malignant tumors of the tongue, those situated posteriorly, and those located on the ventral surface are best destroyed with surgical diathermy."<sup>6</sup>

The commonest site, that is, on the side of the tongue, fortunately is the easiest to treat. Somervell prefers a 4 cm. needle of 3 cm. active length with 2 mg. strength inserted into the anterior part of the tongue and tied over the dorsum of the tongue to 2.5 cm. needle of 1 mg. strength inserted in the back of the tongue and pushed forward. In this technique if the dosage is 1 mg. per 1 cc. of tissue, the needles are left in place for 10 days, but doubling the strength and halving the time is preferable.

Carcinoma of the back of the tongue is often a large soft mass extending to the epiglottis. This growth is usually very radiosensitive, but the insertion of the needles must be done cautiously in order that the patient does not aspirate a piece of the friable tissue to start a lung metastasis. The needle should be long and with a high dosage to shorten the time in the tissue. Insertion can be accomplished from below the jaw, between the facial artery and the angle of the mandible.

When the tip of the tongue is involved, because of its extreme mobility, excision is best with transverse insertion of short needles for radiation of the base. Speech will be little affected by this procedure.<sup>15</sup>

If radium seeds are to be used, 1.5 mc. seeds can be implanted 1 cm. apart. With this technique Jorstad and Verda report 90% of private patients, 30 in number, had no evidence of local recurrence or incomplete regression after 5 years, and in 55 indigent patients, 64% met the same criteria.<sup>9</sup>

Carcinoma of the tonsil and about the epiglottis is the most difficult to treat because of the early metastasis. The tonsil can be treated by insertion of long radium needles below the mucosa in front of the ramus of the mandible—introducing them through the skin and conjointly using Roentgen ray therapy with 400 kv. or greater.

In cases where the first treatment of radiation has not controlled the lesion, or the greater part of the tongue is involved, surgery should be considered.

When the floor of the mouth is involved, radium needles can be introduced from just within the mandible from the outside, and pointed vertically upward—also needles should be inserted parallel to the axis of the tongue from within the mouth. It is probable here that some sequestration of the mandible will result.<sup>15</sup>

If molds are to be used in the floor of the mouth lesions, they should be of the sandwich type with a radium mucosal distance of 0.5 cm. delivering 8000 r. and a skin radium distance of 2 cm. delivering 6000 r. The molds are worn only 8 hours daily for a period of 7 to 8 days.

At the Memorial Hospital of New York, carcinoma of the floor of the mouth is treated preferably by Roentgen ray, using a portal from 3 to 4 cm. in the majority of cases. The cylinder inserted into the mouth holds the tongue upward and backward, this because almost all floor lesions seem to center about the submaxillary duct orifice. Other factors are a target distance of 35 cm. and 200 kv. with 15 to 30 ma., and a filter of 0.5 mm. of copper plus 1 mm. of aluminum. Daily treatment or treatments at least 3 times weekly are given to a total dose of from 5000 to 7500 r. delivered within 20 days. The treatment commonly is supplemented by interstitial radon averaging only up to millicuries and not exceeding 6 mc.<sup>16</sup>

Roentgen therapy has been adopted in this institution because it is believed that interstitial radon seed and radium needle treatment results in too high an incidence of local radionecrosis and osteomyelitis. On the other hand, most roentgenologists will admit that Roentgen rays are ineffective in controlling mouth cancer in their hands.

When the lesion extends to the alveolus surgery is probably necessary.

When the cancer starts on the alveolar ridge and is superficial, H. E. Davis, J. H. Gilmore and M. Baker of Chicago, in a large series, have been able to completely control the lesion with interstitial radon seeds or radium needle molds without clinical evidence of bone radionecrosis.<sup>5</sup> Where this complication has occurred, it can be easily cared for surgically, or by the use of zinc peroxide.<sup>17</sup>

In mandibular cancer, surgery gives the best prognosis. Either resection or wide destruction of the mandible should be performed. If the malignancy has spread to the antrum the sinus must be widely opened so that a radium mold may be used, or the involved region should be destroyed by cautery.

Cancer of the soft palate usually responds well to radiation therapy. The radon seeds may be implanted or contact Roentgen ray employed. In some cases a sandwich mold will be tolerated here and usually a radium plaque can be placed on the superior surface of the soft palate after topical anesthesia.

Hard palate lesions give a good prognosis with surgery.<sup>1</sup>

It is to be noted that the treatments thus far discussed have chiefly been surgical or radiation from radium or radon. An exception was the therapy of floor of the mouth lesions as handled in the New York Memorial Hospital. M. Cutler for several years has been particularly interested in carcinomas which are considered radioresistant. The more resistant area in the center of the lesion receives a greater dosage; from 3 to 5 r. are delivered per minute, and usually 3 fields are used in oral cancer. As much as 1400 r. have been administered in 2 sessions through a port 3 by 3 cm. When radium is used with this concentrated technique 10 gm. are used at a distance of 12.5 cm. with ports varying from 10 to 2 cm. in diameter. In a floor of the mouth squamous cell carcinoma the field used was 6 by 6 cm. and the 10 gm. of radium at a distance of 12.5 cm. was filtered through 1 mm. of platinum. A total of 120,000 mg. hr. was delivered in 12 days in 5000 mg.-hr. doses received twice daily. After 2½ years the patient still had no recurrence.<sup>3,4</sup> It is still too early to evaluate this method of treatment.

With radiation therapy radionecrosis is not uncommon. This is generally painful, the involved area is very tender, healing is slow and sepsis and suppuration usually present. This discouraging picture can be changed by the use of surgery.

The primary lesion in mouth cancer has a good prognosis when cared for by a competent radiotherapist or surgeon trained in oral cancer surgery. However, whether or not the patient survives will in a large measure be determined by how the cervical lymph glands are treated. Distant metastasis is rare in mouth malignancies; the regional glands preventing the spread below the clavicles. A huge cauliflower-like lesion of long duration may have no metastasis, while a small ulcer of the mouth, hard to see, may have caused considerable neck metastasis in a short period. Brown and McDowell, after studying the literature, state that in the past 15 years no 5-year cure of proven malignancy of cervical nodes has been reported with external radiation technique—the only radiation cures being interstitial radiation following access surgery.<sup>2</sup> The burden of the care of the cervical metastasis is therefore the surgeon's lot.

"Block dissections of the neck were never a popular operation with the general surgeon. It is in a field in which he is not called on to work frequently. The procedure is a prolonged one, requiring patience, meticulousness, and enthusiasm about the ultimate result. An intimate knowledge of the anatomy of the neck is required. For these reasons block dissections of the neck have been in many instances a name only, rather than a true description of the method carried out."<sup>10</sup> The problem is, of course, as to when the block neck dissection should be performed. Kennedy quotes Phillips as finding 51.6% of the cases in which a block neck dissection was carried out to have malignant glands in buccal carcinoma, even though none of the cases had clinical nodes. Simmons found 34% of his cases of oral cancer had involved nodes in the series without palpable nodes.

Erich deals with the metastasis even before caring for the primary. Others, such as Butlin, have also handled patients in the same manner. There are two reasons for operating on the neck before caring for the cancer in the mouth: 1. A malignancy in the neck may suddenly change in a few weeks from an operable case to that of a so-called inoperable metastasis.

2. The patient will often not return following a seemingly controlled condition of the primary, and a large number of these will sometimes return later with an inoperable metastasis.

However, the majority of those experienced in oral cancer prefer to treat the mouth lesion first if radiation is to be the form of treatment, and then watch the site of the primary for several weeks in order to evaluate the control of the lesion. If they feel that the tumor is not responding to irradiation they then believe surgery of the neck and of the primary can be combined in one operative procedure. Somervell, who has had personal experience with over 1000 cases of mouth cancers, believes that operation does not have the unpleasant after-effects of radiation, and prefers it except for tongue, cheek and tonsillar lesions. If operations are found to be insufficient in his clinic, they are reinforced by the use of radium. He believes deep Roentgen ray therapy is very disappointing in mouth cases; however, he is probably too pessimistic, for in some institutions deep Roentgen ray therapy is believed to be useful. One must always remember that one cancer cell left behind will kill the patient; a small radium burn or extramutilation may inconvenience the patient, but may save his life.



The study of the statistics of those handling a large number of cases leads one to believe the safest procedure in cheek, tongue and floor of the mouth lesions is to do block neck dissection as early as possible, waiting only to see if the primary is controlled. This procedure should be adopted regardless if nodes are palpable or not. In the case of cheek lesions without palpable nodes, a suprahyoid neck dissection will probably be adequate. In floor or mouth and tongue lesions a complete block neck dissection from the clavicle upwards to the mandible must be undertaken to give the patient even any reasonable security. This should always be done if palpable nodes are present or not. These neck dissections can be done under intratracheal anesthesia or possibly with nerve block infiltration anesthesia. B. Freeman has collected over 500 cases of block neck dissection with the use of nerve block anesthesia, without a single fatality.<sup>7</sup>

"Finally I feel that we should also remember that our duty is to relieve suffering, and often we ought to put that before the actual saving of life. If euthanasia is to be the probable effect of an operation it may be the right thing to do it, and it is, in my opinion, almost better than insufficiency or neglect.

"Perhaps that consideration may make our operation more radical and effectual. There is no excuse for a surgeon who does a shoddy or insufficient operation for malignant disease, least of all in a hospital where radium is available to reinforce operative deficiencies. 'He's had about enough; we had better leave that little bit,' said with the kindest motives, in order to save an extra 2% risk of mortality, may make the death sentence of the patient."<sup>15</sup>

#### REFERENCES

- (1.) Blair, V. P., and Byars, L.: *Texas State J. Med.*, 38, 641, 1943.
- (2.) Brown, J. B., and McDowell, F.: *Trans. South. Surg. Assn.*, 55, 254, 1943.
- (3.) Cutler, M.: *Am. J. Roentgenol. and Ther.*, 51, 739, 1944.
- (4.) Cutler, M.: *J. Am. Med. Assn.*, 117, 1607, 1944.
- (5.) Davis, H. E., Gilmore, J. H., and Baker, M.: Personal communication.
- (6.) Erich, J. B.: *Surg. Clin. North America*, August, 1941.
- (7.) Freeman, B.: Personal communication.
- (8.) Jorstad, L. H.: *South. Med. J.*, 35, 970, 1942.
- (9.) Jorstad, L. H., and Verda, D. J.: *Surg. Clin. North America*, p. 1077, October, 1944.
- (10.) Kennedy, R. H.: *Ann. Surg.*, 114, 813, 1941.
- (11.) Keyes, E. L.: *Am. J. Surg.*, 56, 70, 1942.
- (12.) Martin, C. L.: *Am. J. Roentgenol. and Ther.*, 43, 226, 1940.
- (13.) Nuttall, J. R.: *Brit. J. Radiol.*, 16, 45, 1943.
- (14.) Round Table Discussion: *Canad. Med. Assn. J.*, 50, 556, 1944.
- (15.) Somervell, T. H.: *Brit. J. Surg.*, 32, 35, 1944.
- (16.) Sugarbaker, E. D., and Martin, H. E.: *Gynec. and Obst.*, 71, 347, 1943.
- (17.) Sunderland, D. G., and Binkley, J. S.: *Radiology*, 35, 606, 1940.

## BOOK REVIEWS AND NOTICES

---

AGEING AND DEGENERATIVE DISEASES. Edited by ROBERT A. MOORE, School of Medicine, Washington University. VOLUME XI OF BIOLOGICAL SYMPOSIA, A Series of Volumes Devoted to Current Symposia in the Field of Biology. Edited by JACQUES CATTELL. Pp. 242; 6 ills. Lancaster: Jaques Cattell Press, 1945. Price, \$3.00.

THIS 11th volume, like its predecessors, presents a valuable symposium on an important and timely problem by men experienced in their subject. Of the 12 items, most are from the chemical or experimental laboratory, a few present philosophic or clinical considerations. The list follows: The Relation Between Etiology and Morphology in Degenerative and Sclerosing Arterial Disease, by W. C. Hueper; Arteriosclerosis and Lipid Metabolism, by Irvine H. Page; Research Work on Degenerative Disease, by William B. Kountz; The Glucose Tolerance in the Elderly Patient, by Lilli Hofstatter, Arthur Sonnenberg, and W. B. Kountz; Progeria, Report of a Case, by Alfred S. Schwartz and Jean V. Cooke; Effects of Lesions of the Autonomic Ganglia Associated With Age and Disease, on the Vascular System, by Prof. Albert Kuntz; The Rôle of the Pancreas in Arteriosclerosis, by Prof. Lester R. Dragstedt; Difficulties in Clinical Recognition of Degenerative Diseases, by Edward J. Stieglitz; Correlation of Clinical Knowledge in the Treatment of the Degenerative Diseases, by Prof. William J. Kerr; Age, Change, and the Adopted Life, by Prof. William de B. MacNider; Nutrition and Growth and Their Influence on Longevity in Rats, by John A. Saxton; Some Hormone Action in Relation to the Ageing Process, by Prof. Leo Loeb; Round Table Discussion. As might have been expected, first there is considerable fluctuation in merit in these presentations; and, second, none of the problems of ageing and degenerative diseases have been solved. Nevertheless, those interested in geriatrics—and what physician should not be—will find here much profitable reading.  
E. K.

---

THE PSYCHOLOGY OF WOMEN. A Psychoanalytic Interpretation. By HELENE DEUTSCH, M.D., Associate Psychiatrist, Massachusetts General Hospital; Lecturer, Boston Psychoanalytic Institute. Foreword by STANLEY COBB, M.D., Bullard Professor of Neuropathology, Harvard University. Vol. 1. Pp. 399. New York: Grune & Stratton, 1944. Price, \$4.50; Vol. 2, Motherhood. Pp. 498. Ib., 1945. Price, \$4.50.

THE first volume presents a systematic picture of female instinctual development and its relation to the reproductive function. Emphasis is placed upon the individual emotional experiences and the conflicts connected with them. The aim of the volume is to explain the normal psychic life of women and their normal conflicts. The material forming the basis for the book includes not only the personal observations of the author but records of many other observers, hospital files and records of social agencies. The material is treated from 3 aspects: an exposition of the psychologic life of woman, an analysis of this life, and the non-feminine aspect of femininity. It leaves out of consideration the problem of motherhood. The curriculum of the medical student includes no time allotted to the study of the emotional conflicts of women, and yet the practitioner meets such problems almost daily. This volume by Deutsch includes many interesting observations upon the nature of the thinking of women, which should hold the attention of physicians who are brought into contact with the psychologic problems of their female patients. The second volume, on Motherhood, deals primarily with the normal conflicts which occur in connection with sterility, abortion, pregnancy, delivery

and laetation. It also includes a consideration of the mother-child relationship, unmarried mothers, adoptive mothers and stepmothers. This book contains many instructive case records which deal with the everyday problems of the practising physician, and consequently should be very helpful to both the obstetrician and the general practitioner. The author treats at some length the question of psychogenic sterility. If the psychic state of the patient forbids the consummation of the sex act, the resulting sterility might well be considered of psychic origin. However, since recent studies are showing the existence of a high incidence of non-ovulation occurring in women who otherwise have been found to be normal, as are their husbands, the Reviewer must remain skeptical regarding the rôle played by the mind as the cause of sterility where intercourse is practised.

D. M.

---

OFFICE ENDOCRINOLOGY. By ROBERT B. GREENBLATT, B.A., M.D., C.M., Professor of Experimental Medicine, University of Georgia School of Medicine; Director, Sex Endocrine Clinic, University Hospital, Augusta, Ga. Foreword by G. LOMBARD KELLY, M.D., Dean, University of Georgia School of Medicine. Second Ed. Pp. 243; many figs. Springfield, Ill.: Charles C Thomas, 1944. Price, \$4.00.

THIS small volume is based upon a series of lectures delivered to a post-graduate class in office endocrinology. Two-thirds of the volume deal with the female, one-third with the male. The volume does not pretend to be comprehensive. Its brevity and its emphasis upon therapy should recommend it to the busy practitioner. Small volumes frequently brought up to date have a very definite place in the library of all practising physicians.

D. M.

---

THE MEDICAL CLINICS OF NORTH AMERICA. Symposium on New Developments in Medicine. Pp. 561; 96 figs. Philadelphia: W. B. Saunders, 1945. \$16 per year.

AN excellent and timely review of modern therapeutic agents and methods, this issue comprises clinics from 5 major medical centers in the United States. Of especial interest is the article on cirrhosis of the liver, in which is presented an enlightening and hopeful approach to a very difficult therapeutic problem. Correlated with this article is a clinic in which liver biopsy is elucidated as a safe and very helpful diagnostic procedure. Another clinic not to be missed is that on the diagnosis and treatment of various pleural effusions.

J. W.

---

THE MANAGEMENT OF OBSTETRIC DIFFICULTIES. By PAUL TITUS, M.D., Obstetrician and Gynecologist to the St. Margaret Memorial Hospital, Pittsburgh; Secretary of the American Board of Obstetrics and Gynecology; Comdr. (MC) USNR, attached to Professional Division, Bur. Med. and Surg., Navy Dept., Washington, D. C. Pp. 1000; 426 ills. and 8 color plates. Third Ed. St. Louis: C. V. Mosby, 1945. Price, \$10.00.

TITUS' excellent volume, in this 3rd edition, includes revisions in many subjects: Roentgen ray pelvimetry, toxemia, caudal anesthesia, the technique of extraperitoneal Cesarean section, and considers at some length the use of penicillin. To those who are familiar with the earlier editions the present one needs no recommendation.

D. M.

---

THOUGHTS, DEEDS AND HUMAN HAPPINESS. By K. W. MONSARRAT. Pp. 123. London: Hodder & Stoughton, 1944. Price, \$1.50.

THIS book which is a sequel to one that was chiefly an analysis of human self-expression, is for the most part concerned with the question: Upon what should we rely in planning for what we desire, and is there a principle of behavior worthy of our confidence? The chapters are, Self-Expression; The

Human Self's Performance; The Energy-Matter Puzzle; The Mind-Body Puzzle; Interpretive Events; The Relative Principle; The Earth and Its Inhabitants; The Living and Non-Living Puzzle; Evolution in the Animal Kingdom to Man; Judgments of Value; Design for Living.

The text is presented in a way that does not lend itself to review readily. The words "Sense" and "Intelligence" are prominent throughout the entire work. By the former is meant the ability which gives one views or pictures; the latter implies the interpretation of those views in terms of actions that have produced what the views show. Confidence in these as complements to our desires will afford verdicts that are reliable as to judgments on terrestrial affairs. Coördination, not compulsion, is urged. We should be generous to each other, even giving to the other the wherewithal for the life that he prefers. It should not be "live and let live," but "live and give."

At the time when man's greatest efforts are directed toward the killing of man and the destruction of property, this noble sentiment of universal generosity comes like a gleam of light piercing the world's encircling darkness.

N. Y.

**HANDBOOK OF PRACTICAL BACTERIOLOGY, A GUIDE TO BACTERIOLOGICAL LABORATORY WORK.** By T. J. MACKIE and J. E. MCCARTNEY. Seventh Ed. Pp. 720. Baltimore: Williams & Wilkins, 1945. Price, \$5.00.

THE book is rather small, the pages being only  $4\frac{1}{2}$  by  $7\frac{1}{4}$  inches. The subject matter deals entirely with the practical aspects of bacteriology. In addition to bacteria it includes material on spirochetes, fungi, rickettsiae, filterable viruses and animal parasites. While the book undoubtedly is of value to workers in the British Kingdom, workers in the United States will find little use for it as the procedures are different from those ordinarily used and regarded as "standard technic" in this country.

H. M.

**REFRACTION OF THE EYE.** By ALFRED COWAN, M.D., Professor of Ophthalmology, Graduate School of Medicine, University of Pennsylvania; Attending Ophthalmologist, Philadelphia General Hospital; Consulting Ophthalmologist, Council for the Blind and Supervising Ophthalmologist of the Department of Public Assistance, Commonwealth of Pennsylvania. Pp. 278; 172 engravings and 3 colored plates. Second Ed. Philadelphia: Lea & Febiger, 1945. Price, \$4.75.

THIS 2nd edition is very similar to the first. The subject matter, as in the 1st edition, is divided into 19 chapters dealing chiefly with the theory of optics and clinical refraction. A few sections such as the one on Aniseikonia, the use of cycloplegia and the bibliography have been enhanced. Many paragraphs have been rewritten, but with very little change in text. The 2nd edition has the same size, but fewer pages than the first. There are more lines on each page so that the book is thinner.

F. A.

**A HANDBOOK OF PSYCHIATRY.** By LOUIS J. KARNOSH, B.S., Sc.D., M.D., Associate Clinical Professor of Nervous Diseases, School of Medicine, Western Reserve University; Director of Neuropsychiatry, City Hospital, Cleveland; Consulting Neuropsychiatrist, Cleveland Clinic; and EDWARD M. ZUCKER, A.B., M.D., Clinical Instructor in Nervous Diseases, Western Reserve School of Medicine; Associate in Neuropsychiatry at Cleveland City Hospital. Pp. 302; 40 figs. St. Louis: C. V. Mosby, 1945. Price, \$4.50.

WRITTEN for the general practitioner and medical student, the more prominent positions in the book are given to the manic-depressive psychoses, involutional psychoses, schizophrenia, paranoid states, and the psychoneuroses. The organic reaction types include psychoses with syphilis of the central nervous system, the traumatic psychoses, psychoses with brain tumor and other brain diseases, psychoses with cerebral arteriosclerosis, and senile

psychoses. Included in the discussion on psychosomatic medicine are the effects of repressed feelings on bodily functions, factors in cardiac disorders, gastro-intestinal disturbances and respiratory disturbances, and organic susceptibility. Since most subjects with psychopathic personalities do not become interned in mental hospitals or jails, many showing this troublesome disorder are at large; and since the general practitioner must deal with them often, a more comprehensive consideration of these disturbers would prove helpful. The final chapters discuss psychiatry and the law and mental hygiene. The text finds fulfillment of the purposes stated in the Preface. A glossary is included.

---

N. Y.

A BIBLIOGRAPHY OF VISUAL LITERATURE. By JOHN F. FULTON. Pp. 117. Springfield, Ill.: Charles C Thomas, 1945. Price, \$3.00.

THIS book is patterned on the 2 volumes, "Bibliography of Aviation Medicine" which appeared in 1942 and 1944. It is extremely useful as a guide to recent literature, particularly as many of the articles abstracted are from other than ophthalmologic journals. Attention has naturally been concentrated on the biologic aspects of ophthalmology and the book does not intend to be complete in all phases of general ophthalmology or ocular pathology. The indexing is so complete that much time will be saved by anyone looking up the literature on a particular subject.

F. A.

DOCTORS AT WAR. Edited by MORRIS FISHBEIN, M.D. Pp. 418; fully illustrated. New York: E. P. Dutton, 1945. Price, \$5.00.

THIS important statement of various aspects of the American Medical effort in the present war is made by 16 well qualified authorities. In a form of presentation that should interest both layman and medico, it gives a stirring picture of what American military and civil medicine are accomplishing today. As to selection of draftees, and their training, to men in action and rehabilitation, to the prevention and treatment of disease in the army, navy, industry and the home, the record is one of which we all may be proud—the one thing we should all know more about. Though good use is made of the 400 pages and one finds a considerable amount of factual and statistical matter included, the book could hardly be more than a bird's-eye view; but it is a good one and an authoritative well-balanced presentation of an important phase of the war effort, and one of which our profession and the country at large can be most proud.

E. K.

## NEW BOOKS

*The History of Surgical Anesthesia.* By THOMAS E. KEYS. With an Introductory Essay by CHAUNCEY D. LEAKE and a concluding chapter, *The Future of Anesthesia* by NOEL A. GILLESPIE. Pp. 191. New York: Schuman's, 1945. Price, \$6.00.

*Bacillary Dysentery, Colitis and Enteritis.* By JOSEPH FELSEN, B.A., M.D., Director of Medical Research, Bronx Hospital, New York; Director of International and Pan-American Dysentery Registry. Pp. 618 with 145 ills.. Phila.: Saunders, 1945. Price, \$6.00.

*The Story of a Country Medical College.* A History of the Clinical School of Medicine and The Vermont Medical College, Woodstock, Vt., 1827-1856. By FREDERICK CLAYTON WAITE. Pp. 213. Montpelier, Vt.: Vermont Historical Society, 1945. Price, \$4.50.

*The Care of the Neurosurgical Patient—Before, During and After Operation.* By ERNEST SACHS, A.B., M.D., Professor of Clinical Neurological Surgery, Washington Univ. School of Medicine, Saint Louis, Mo. Pp. 268; 177 ills, including 2 in color. St. Louis: Mosby, 1945. Price, \$6.00.

*A Primer of Electrocardiography.* By GEORGE BURCH, M.D., F.A.C.P., Assoc. Professor of Medicine, Tulane Univ. School of Medicine; Senior Visiting Physician, Charity Hospital, New Orleans; and TRAVIS WINSOR, M.D., Instructor in Medicine, Tulane Univ. School of Medicine; Assistant Visiting Physician, Charity Hospital, New Orleans, La. Pp. 215; 235 engravings. Phila.: Lea & Febiger, 1945. Price, \$3.50.

*Government in Public Health.* By HARRY S. MUSTARD, B.S., M.D., LL.D., DeLamar Professor of Public Health Practice and Director, School of Public Health, Faculty of Medicine, Columbia Univ. Pp. 219. New York: Commonwealth Fund, 1945. Price, \$1.50.

*The Physiology of the Newborn Infant.* By CLEMENT A. SMITH, M.D., Professor of Pediatrics, Wayne Univ. College of Medicine; Medical Director, The Children's Hospital of Michigan. Pp. 312. Springfield, Ill.: Thomas, 1945. Price, \$5.50.

*Student's Guide in Nursing Arts.* By M. ESTHER McCLAIN, R.N., B.S., M.S., Assistant Professor in Nursing Education, and Instructor in Nursing Arts of the Providence Division of the School of Nursing Education, The Catholic University of America, Washington, D. C.; formerly Instructor of Nursing Arts, St. Vincent's Hospital, Indianapolis. Pp. 407. St. Louis: Mosby, 1945. Price, \$3.00.

*The Falling Sickness.* A History of Epilepsy From the Greeks to the Beginnings of Modern Neurology. By OWSEI TEMKIN, M.D., Associate Professor of the History of Medicine at The Johns Hopkins University. Pp. 380. Baltimore: The Johns Hopkins Press, 1945. Price, \$4.00.

*The Medical Clinics of North America.* Mayo Clinic Number. Symposium on Medical Emergencies. Pp. 1067; 160 figs. Phila. and London: Saunders, 1945.

## NEW EDITIONS

*Clinical Biochemistry.* By ABRAHAM CANTAROW, M.D., Professor of Physiological Chemistry, Jefferson Medical College; formerly Associate Professor of Medicine, Jefferson Medical College, and Assistant Physician, Jefferson Hospital; and MAX TRUMPER, Ph.D., Lt. Comdr., H(S), USNR, Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md. Third Ed. Pp. 647. Phila.: Saunders, 1945. Price, \$6.50.

*Effective Living.* By C. E. TURNER, A.M., Ed.M., Sc.D., Dr.P.H., Professor of Public Health, Massachusetts Institute of Technology; formerly Associate Professor of Hygiene, Tufts Medical and Dental Schools; and ELIZABETH McHose, B.S., M.A., Director of Physical Education for Girls and Chairman of the Health Council, Senior High School, Reading, Pa. Second Ed. Pp. 432; 164 ills. St. Louis: Mosby, 1945. Price, \$2.00.

*Textbook of Bacteriology.* By EDWIN O. JORDAN, Ph.D., late Professor of Bacteriology, Univ. of Chicago. Revised by WILLIAM BURROWS, Ph.D., Assoc. Professor of Bacteriology, Univ. of Chicago. Pp. 909; 242 ills. Fourteenth Ed. Phila.: Saunders, 1945. Price, \$7.00.

*Diseases of the Breast.* By CHARLES F. GESCHICKTER, M.A., M.D., Lt. Comdr., MC, USNR, Director of The Francis P. Garvan Cancer Research Laboratory; Pathologist, St. Agnes Hospital, Baltimore. With a Special Section on Treatment in collaboration with MURRAY M. COPELAND, A.B., M.D., F.A.C.S., Instructor in Surgery, Johns Hopkins Medical School. Second Ed. Pp. 826; 593 ills. Phila.: Lippincott, 1945. Price, \$12.00.

*Intravenous Therapy.* By K. V. THAKKAR (Bombay University), Late Chief Medical Officer to the States of Palitana and Idar. Second Ed. Pp. 349; 10 ills. Bhavnager, Kathiawar: K. V. Thakkar, Medical Bldg., Mama Kotha Rd., 1944.

*Fractures of the Jaws.* By ROBERT H. IVY, M.D., D.D.S., F.A.C.S., Professor of Plastic Surgery, School of Medicine and Graduate School of Medicine, and of Clinical Maxillo-Facial Surgery, School of Dentistry, University of Pennsylvania; Chief of Plastic Surgery, Graduate Hospital; and LAWRENCE CURTIS, M.D., D.D.S., F.A.C.S., Assistant Professor of Plastic Surgery, Graduate School of Medicine. Third Ed. Pp. 174; 199 engravings. Phila.: Lea & Febiger, 1945. Price, \$4.50.

*Nitrous Oxide-Oxygen Anesthesia.* By F. W. CLEMENT, MAJOR, M.C., A.U.S., formerly Director of Anesthesia at Flower Hospital, The State Hospital for the Insane, Lucas County Hospital, Toledo Dental Dispensary; Anesthetist to Toledo, Mercy and St. Vincent's Hospitals, Toledo, Ohio. Second Ed. Pp. 288; 92 engravings. Phila.: Lea & Febiger, 1945. Price, \$4.50.

*Clinical Parasitology.* By CHARLES FRANKLIN CRAIG, M.D., M.A. (HON.), F.A.C.S., F.A.C.P., COL., U.S.A. (R.), D.S.M., formerly Director, Army Medical School, and Assistant Commandant, Army Medical Center, Washington, D. C.; and ERNEST CARROLL FAUST, M.A., PH.D., Professor of Parasitology in the Department of Tropical Medicine, Tulane Univ. of Louisiana, New Orleans, La.; Consultant to the Secretary of War, Army Epidemiologic Board on Epidemic and Tropical Diseases. Fourth Ed. Pp. 871; 305 ills.; 4 colored plates. Phila.: Lea & Febiger, 1945. Price, \$10.00.

*The Intervertebral Disc.* By F. KEITH BRADFORD, M.D., Houston, Texas; and R. GLENN SPURLING, M.D., Louisville, Ky. Second Ed. Pp. 192. Springfield, Ill.: Thomas, 1945. Price, \$4.00.

---

#### NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMHAAER, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles, arranged alphabetically according to the name of the first author and should be complete that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

During the emergency 150 REPRINTS will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150.

# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

NOVEMBER, 1945

## ORIGINAL ARTICLES

### HOMOLOGOUS SERUM HEPATITIS AND INFECTIOUS (EPIDEMIC) HEPATITIS

#### EXPERIMENTAL STUDY OF IMMUNITY AND CROSS IMMUNITY IN VOLUNTEERS

##### A PRELIMINARY REPORT

BY CAPT. JOHN R. NEEFE, M.C., A.U.S.

JOSEPH STOKES, JR., M.D.

AND

CAPT. SYDNEY S. GELLIS, M.C., A.U.S.

PHILADELPHIA, PENNSYLVANIA.

(From the Department of Pediatrics, School of Medicine, University of Pennsylvania,  
and the Hospital of the University of Pennsylvania)

THE high incidence of infectious (epidemic) hepatitis and homologous serum hepatitis during the present war has stimulated extensive investigations of these two diseases. Unfortunately all attempts to isolate, identify and cultivate the causative agents have failed as have efforts to develop specific serologic or other tests and to find a susceptible animal. For these reasons, the relationship between homologous serum hepatitis and infectious (epidemic) hepatitis has remained obscure. Nevertheless, considerable information has been obtained. Certain similarities between the two diseases and their causative agents have been noted.<sup>2,5,6,9</sup> The causative agents of the two diseases both pass through bacteria trapping filters and survive heating at 56° C. for at least 30 minutes. They also produce similar clinical manifestations during the active disease and the pathologic changes apparently are the same. Both agents are present in the blood at some stages of the respective diseases. On the other hand, certain differences have been observed.<sup>9,10</sup> Infectious (epidemic) hepatitis usually, but not always, is associated with elevation of temperature above 100° F., whereas the temperature with homologous serum hepatitis usually does not exceed 100° (oral). In infectious hepatitis, the interval from exposure to jaundice usually is less than 40 days, whereas the interval from inoculation to jaundice in homologous serum hepatitis



usually is 60 or more days. Transmission of the causative agent to other persons by means other than injection of blood products is common from cases of infectious (epidemic) hepatitis but is rare from cases of homologous serum hepatitis. The causative agent of infectious hepatitis commonly is present in the feces of persons with this disease and produces the disease when administered by the oral route. However, the only reported attempt to transmit homologous serum hepatitis by the oral administration of feces from persons with this disease indicated that the agent either was not present in the feces or, if present, was not effective when administered by the gastro-intestinal route.<sup>11</sup>

The observations cited above, though suggestive of some difference in the causative agents of infectious hepatitis and homologous serum hepatitis, do not provide satisfactory evidence that the agents are different.

In order to obtain additional information on the relationship of these agents, a study of their antigenic properties, as indicated by immunity and cross immunity studies in human volunteers, was undertaken in 1943. Since that time, several papers dealing directly or indirectly with this subject have been published. A brief consideration of these data is pertinent to the present report.

*Homologous Immunity in Infectious (Epidemic) Hepatitis.* Camcron<sup>1</sup> has reported that second attacks (not relapses) of infectious hepatitis have been uncommon in Palestine where the disease is endemic. Findlay and his associates,<sup>3</sup> after a survey of 792 officers and 1822 enlisted men, came to the conclusion that one attack of infectious hepatitis probably produces considerable, but not absolute, immunity. Finally the infrequent occurrence of the disease in persons over 35 years of age, as compared with the relatively high incidence in children and young adults, suggests the former have acquired immunity from previous apparent or inapparent infections. To date, no adequate experimental study of homologous immunity following infectious hepatitis has been reported. However, the epidemiologic data suggest that one attack of infectious hepatitis is followed by some degree of homologous immunity.

*Homologous Immunity in Homologous Serum Hepatitis.* Apparently the only reported data on homologous immunity resulting from an attack of homologous serum hepatitis are those of Oliphant.<sup>14</sup> Twelve to 18 months after hepatitis produced by an agent in experimentally injected yellow fever vaccine (containing human serum) or in ictero-genic human serum alone, 10 persons were reinjected with the yellow fever vaccine. At the same time, 10 apparently normal controls without history of previous hepatitis were injected with the same vaccine. Three of the 10 controls subsequently developed jaundice but none of those who previously had had serum hepatitis again developed the disease. These results suggest that the first attack of serum hepatitis was followed by immunity to the same hepatitis agent.

*Cross-immunity Between Infectious Hepatitis and Homologous Serum Hepatitis.* The reported data on cross-immunity are conflicting.

McFarlan and Chesney,<sup>7</sup> in the study of an army unit involved in an outbreak of homologous serum hepatitis following the prophylactic injection of a mumps convalescent plasma, found that 11 of the 175 injected men had a history of naturally occurring jaundice (probably infectious hepatitis) in childhood. Eight of these 11 men again developed jaundice following the injection of the mumps convalescent plasma. Thus the previous attack of naturally occurring jaundice did not protect against subsequent homologous serum hepatitis. In contrast, the epidemiologic investigations of Findlay and his associates<sup>3</sup> gave them the impression that persons who previously had had infectious hepatitis were less susceptible to serum hepatitis than normal persons. Their data, however, do not seem convincing. Concerning the occurrence of these two diseases in the reverse order, Gordon is quoted by Witts<sup>11</sup> as having observed that previous homologous serum hepatitis not only failed to protect against subsequent infectious hepatitis but may have increased the susceptibility to the latter disease. The data of Gordon were not described. On the other hand, the results of Oliphant's experimental study<sup>14</sup> suggested that homologous serum hepatitis was followed by immunity that also protected against an agent of infectious hepatitis. The ages of Oliphant's subjects were not mentioned, a factor which is of considerable importance in the interpretation of the results because of the decreased susceptibility of persons over 35 years of age to infectious hepatitis.

*Protection by Human Immune Serum (Gamma) Globulin.* The ability of human immune serum globulin to prevent or attenuate infectious (epidemic) hepatitis<sup>4,15</sup> indicates that large pools of human adult plasma may contain a protective substance which neutralizes or inactivates the causative agent. As human immune serum globulin is the fraction of blood plasma which contains specific antibodies for the causative agents of a variety of diseases, it is probable that the substance protecting against the agent of infectious hepatitis is a specific antibody present as a result of previous apparent or inapparent infection of the plasma donors. This globulin fraction contains many different antibodies and therefore might include antibodies for several hepatitis agents. For this reason, the protective properties of human immune serum globulin probably will not aid in solving the question of one or multiple causative agents of hepatitis.

The available immunologic data thus suggest that both infectious (epidemic) hepatitis and homologous serum hepatitis are followed by some degree of homologous immunity but the presence or absence of cross-immunity between the two diseases has not been established. Factors which may lead to erroneous interpretation of cross-immunity data and which may be responsible for the conflicting results reported to date include: (a) lack of knowledge of the sources of the hepatitis agents involved; (b) variation in susceptibility to infectious (epidemic) hepatitis with age; (c) uncertainty of the diagnosis or type of previous hepatitis based on history; (d) the probably frequent occurrence of unrecognized hepatitis without jaundice which may be followed by immunity; (e) the lack of knowledge of the presence of homologous

immunity in persons concerned in cross-immunity studies; (f) lack of knowledge concerning the duration of homologous immunity, assuming it exists. Although it is impossible to control all of these factors with the limited methods of study now available, an attempt has been made, in the present investigation, to eliminate as many of them as possible. Because the results to date have provided additional information, a preliminary report is presented at this time. The final results of this and related studies now in progress will be reported later.

**Materials and Methods.** In a previous report,<sup>10</sup> the data pertaining to the first stage of the experiment, namely, the basis for selection of volunteers, the initial experimental conditions, the methods of study, and the materials used for the experimental induction of homologous serum hepatitis, were fully described. After recovery from this disease, 6 of the subjects, ranging in age from 20 to 27 years, volunteered for tests of immunity and cross-immunity. With 1 exception, none of them had recognized hepatitis prior to participation in the first stage of the experiment. In 1939 while attending a university in Connecticut, subject H. J. C. had had a typical attack of "catarrhal jaundice," the onset occurring approximately 1 month after exposure to another student with this disease.

Subjects R. R. M. and C. R. L. first were inoculated\* parenterally with plasma A,<sup>10</sup> a pooled mumps convalescent plasma known to contain a causative agent of homologous serum hepatitis. Subjects N. H. H. and J. C. first were inoculated with plasma B,<sup>10</sup> which was obtained from another volunteer 23 days after his inoculation with plasma A. Subjects S. B. E. and H. J. C. were inoculated first with a yellow fever vaccine<sup>10</sup> which also was known to contain a causative agent of homologous serum hepatitis. One of the donors, whose plasma was included in plasma A, previously had received an injection of one of the lots of yellow fever vaccine that had been followed by hepatitis in a number of recipients.<sup>8</sup> This donor developed hepatitis about 6 weeks after his plasma had been collected. It appears probable, therefore, that the same hepatitis agent was present in plasma A, plasma B, and the yellow fever vaccine. After recovery from hepatitis induced by parenteral administration of one of the 3 materials mentioned above, these 6 men were inoculated parenterally with plasma A (second inoculation; immunity test). After 190 to 218 days, they were inoculated (third inoculation; cross-immunity) with feces pool 1 FIH (1 subject, oral inoculation) or serum pool 2 SIH (5 subjects; parenteral inoculation). These materials, described elsewhere in detail,<sup>12</sup> contained a causative agent of infectious (epidemic) hepatitis that was responsible for an epidemic in a civilian summer camp located in Pennsylvania. 192 days after recovery from the hepatitis that followed his third inoculation, subject R. R. M. was reinoculated with feces pool 1 FIH. Sufficient time has not yet elapsed to carry out the final phase of this experiment, namely, reinoculation with the causative agent of infectious hepatitis, on the other 5 subjects.

At approximately the same time that the men received their second inoculations (plasma A; immunity test), 3 normal controls were inoculated parenterally with plasma A. In addition, 6 other normal persons who received this

\* The term "inoculated" is used herein to indicate either oral or parenteral administration. The term "normal controls" is used to designate volunteers who had no previous history of hepatitis and had received no previous experimental inoculation with materials known to contain a hepatitis agent. The term "hepatitis with jaundice" is used to indicate hepatitis during which icterus was visible at some stage of the disease. Cases with clinical and laboratory evidence of hepatitis but without visible icterus have been designated as "hepatitis without jaundice." "Recovery" is used here to indicate absence of symptoms and physical signs and ability to return to usual duties.

plasma at other times also served as controls. At approximately the same time that those in the test group were inoculated parenterally with serum pool 2 SIH (third inoculation; cross-immunity), 3 normal controls were inoculated parenterally and 3 others were inoculated orally with this serum pool.

After each of the inoculations, the volunteers were observed carefully for symptoms and signs of any illness. Liver function studies were performed 2 or more times weekly.

**Results.** The results of the liver function studies and the approximate duration of symptoms following the three inoculations of the men tested for immunity and cross-immunity are shown in Figures 1 to 6. The results in these men and the controls are summarized in Table 1.

TABLE 1.—RESULTS OF IMMUNITY AND CROSS-IMMUNITY TESTS

Subjects	First inoculation			Second inoculation immunity test			Third inoculation cross-immunity test		
	Agent	Route	Hepatitis	Agent	Route	Hepatitis	Agent	Route	Hepatitis
R. R. M. . .	S.H. Plasma A	Par.	4+	S.H. Plasma A	Par.	0	I.H. Pool 1 FIH	Oral	3+
C. R. L. . .	S.H. Plasma A	Par.	4+	S.H. Plasma A	Par.	?	I.H. Pool 2 SIH	Par.	3+
N. H. H. . .	S.H. Plasma B	Par.	2+	S.H. Plasma A	Par.	?	I.H. Pool 2 SIH	Par.	2+
J. C. . . .	S.H. Plasma B	Par.	1+	S.H. Plasma A	Par.	?	I.H. Pool 2 SIH	Par.	2+
S. B. E. . .	S.H. Y.F.V.	Par.	3+	S.H. Plasma A	Par.	?	I.H. Pool 2 SIH	Par.	1+
H. J. C.* . .	S.H. Y.F.V.	Par.	2+	S.H. Plasma A	Par.	?	I.H. Pool 2 SIH	Par.	0
9 controls . .				S.H. Plasma A	Par.	8 (3 to 4+)			
12 controls .							I.H.	{ 6 Oral 5 (3 to 4+) 6 Par. 0	

NOTE.—S.H., agent of homologous serum hepatitis; I.H., agent of infectious (epidemic) hepatitis; Par., parenteral; 0 indicates no evidence of hepatitis; ? indicates the occurrence of transient symptoms and/or laboratory findings suggestive of transient mild hepatic disturbance; 1+ indicates hepatitis without jaundice; characteristic symptoms associated with significant changes in hepatic function; 2+ indicates hepatitis without jaundice, the clinical and laboratory manifestations being more marked than those designated 1+; 3+ indicates hepatitis with overt jaundice; 4+ indicates hepatitis with overt jaundice, the manifestations being more marked than those designated as 3+.

\* H. J. C. had infectious hepatitis 4 years prior to participation in these experiments.

*Subject R. R. M.* (Fig. 1.) (1) *First inoculation*: 75 days after he was injected parenterally with the serum hepatitis agent (plasma A, 12 ml.), he developed moderately severe hepatitis with jaundice. (2) *Second inoculation (immunity test)*: 154 days after the first inoculation and 34 days after recovery from the first attack of hepatitis, he again was injected parenterally with the same agent of serum hepatitis (plasma A, 10 ml.). No symptoms, physical signs, or laboratory evidence of hepatic disturbance were detected during the subsequent 194 days. (3) *Third inoculation (cross-immunity)*: 194 days after the second inoculation, he was inoculated orally with the causative agent of infectious (epidemic) hepatitis (feces pool 1 FIH, 5 ml.). After an incubation period of 25 days, he developed hepatitis with jaundice. (4) *Fourth inoculation* (not shown in Fig. 1): 270 days after the third inoculation and 192 days after recovery, he again was inoculated orally with the same agent of infectious hepatitis (feces pool 1 FIH). No evidences of hepatitis have been detected during the 100 days which have elapsed.

*Subject C. R. L.* (Fig. 2.) (1) *First inoculation*: approximately 100 days after his initial parenteral injection with the agent of serum hepatitis (plasma A,

9 ml.) he developed moderately severe hepatitis with jaundice. (2) *Second inoculation (immunity test)*: 223 days after the first inoculation and 85 days after recovery he again was injected parenterally with the same agent of serum hepatitis (plasma A, 5 ml.). Between the 57th and 61st days following the second injection, he experienced malaise, generalized aches and pains, mild anorexia and nausea, and 1 episode of vomiting. The symptoms were mild but were associated with a transient slight increase in bromsulphalein retention and slight increase in the excretion of urine urobilinogen. After the 61st day, he felt perfectly well and had no evidence of hepatic disturbance other than occasional weakly positive tests for bilirubin in the urine. (3) *Third inoculation (cross-immunity test)*: 218 days after the second inoculation, he was injected parenterally with the agent of infectious hepatitis (serum pool 2 SIH, 2 ml.). After an incubation period of 28 days, he developed hepatitis with jaundice.

## R. R. M.

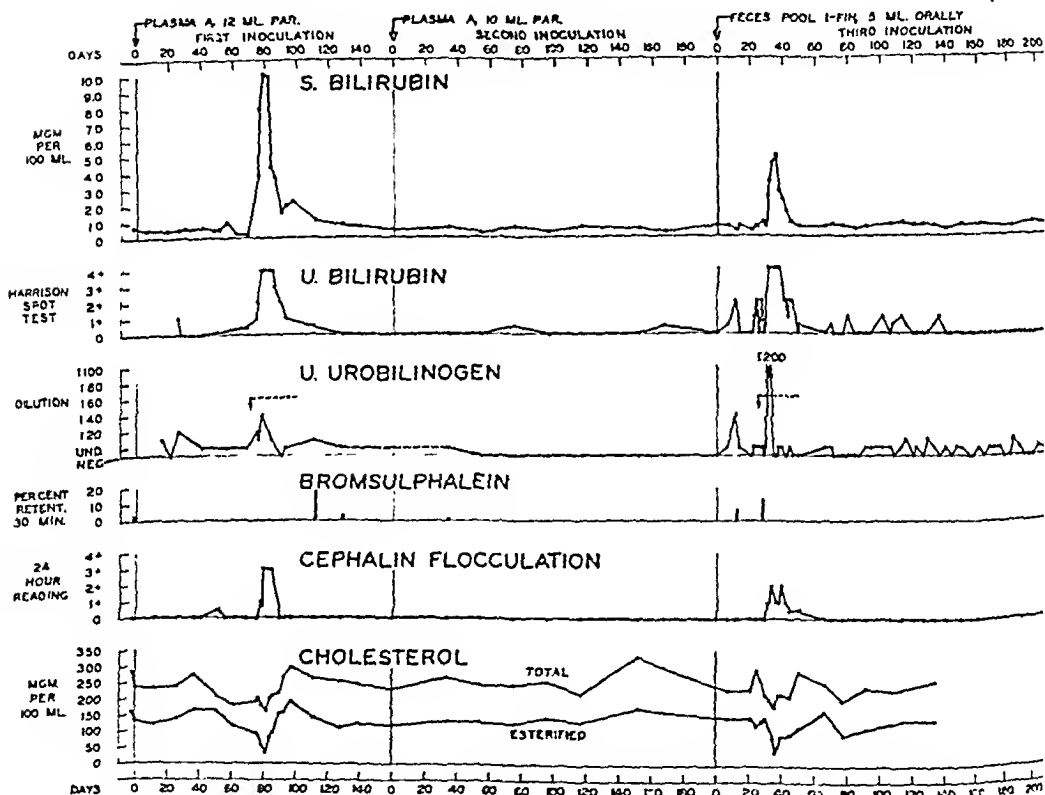


FIG. 1.—Laboratory data on R. R. M. in relation to the initial inoculation with a causative agent of serum hepatitis, the reinoculation with the same agent, and the subsequent inoculation with the causative agent of infectious hepatitis. Arrows and broken horizontal lines above the curve for urine urobilinogen indicate periods during which symptoms were present. "Par." indicates parenteral administration. Sections of curves for various tests shown by broken lines represent relatively long intervals during which no determinations were made. Readings between 0 and 1+ shown for the cephalin cholesterol flocculation test and the Harrison spot test for urine bilirubin indicate responses of questionable significance.

*Subject N. H. H.* (Fig. 3.) (1) *First inoculation*: from the 22nd to the 155th day after parenteral injection of an agent of homologous serum hepatitis (plasma B, 20 ml., probably containing the same agent as plasma A), he had laboratory evidence of mild hepatitis without jaundice. Malaise, anorexia

and nausea were present from the 23rd to the 26th day. After the 26th day, he felt perfectly well in spite of the continued positive laboratory evidence of hepatic disturbance. (2) *Second inoculation (immunity test)*: 240 days after the first inoculation and 85 days after recovery, he again was injected parenterally with the serum hepatitis agent (plasma A, 5 ml.). Between the 83rd and 160th day after this injection, he had laboratory evidence suggestive of subclinical hepatic disturbance without jaundice. Malaise, weakness, easy fatigue, anorexia, nausea, vomiting and abdominal discomfort appeared on the 93rd day but these symptoms persisted for only 24 hours. After the 94th day he felt perfectly well. (3) *Third inoculation (cross-immunity test)*: 218 days after the second inoculation, he was injected parenterally with the agent of infectious hepatitis (serum pool 2 SIH, 2 ml.). After an incubation period of 37 days, he developed typical symptoms and conclusive laboratory evidence of hepatitis without jaundice.

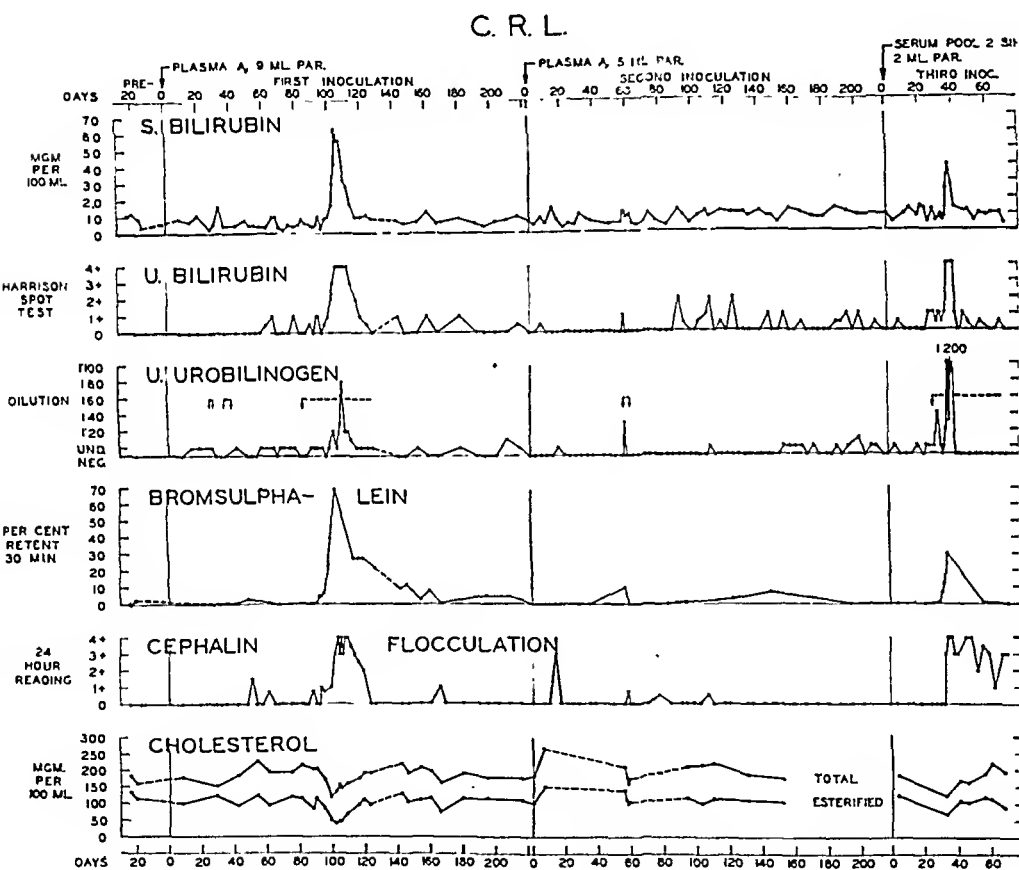


FIG. 2.—Laboratory and other data on subject C. R. L. (See Fig. 1 for legend.)

*Subject J. C. (Fig. 4.)* (1) *First inoculation*: from the 12th to the 62nd day after parenteral injection of the serum hepatitis agent (plasma B, 11 ml.), he had laboratory evidence of mild hepatitis without jaundice. Malaise, anorexia and nausea were present between the 12th and 14th and the 22nd to the 24th days. After the 24th day he felt perfectly well. (2) *Second inoculation (immunity test)*: 196 days after the first inoculation and 172 days after recovery, he again was injected parenterally with the serum hepatitis agent (plasma A, 5 ml.). On the 141st day after this injection, he had malaise, and complained of weakness, easy fatigue, chilly sensations, pain in the back,

anorexia and abdominal discomfort. His temperature was elevated to 99.5° F. (oral). Most of the symptoms, which were associated with weakly positive tests for urine bilirubin, disappeared within 48 hours. No further symptoms or laboratory evidence of hepatic disturbance occurred after the 142nd day. (3) *Third inoculation (cross-immunity test)*: 218 days after the second inoculation, he was injected parenterally with the agent of infectious hepatitis (serum pool 2 SH, 2 ml.). After an incubation period of 28 days he developed symptoms and conclusive laboratory evidence of hepatitis without jaundice.

## N. H. H.

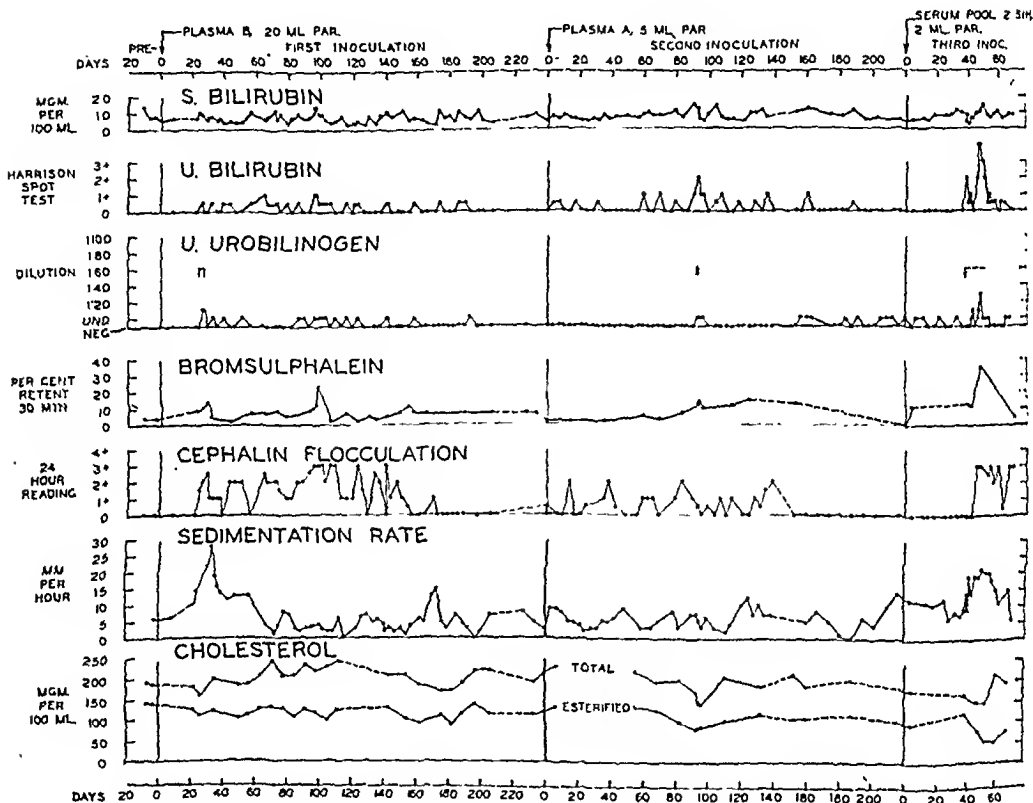


FIG. 3.—Laboratory and other data on subject N. H. H. (See Fig. 1 for legend.) Plasma B and plasma A presumably contained the same causative agent of homologous serum hepatitis.

*Subject S. B. E. (Fig. 5.)* (1) *First inoculation*: between the 75th and 150th day after parenteral injection with a serum hepatitis agent (yellow fever vaccine, 2 ml., probably containing the same agent as plasma A and B), he had symptoms and/or laboratory evidence of hepatitis. Jaundice was apparent from the 95th to the 107th day. (2) *Second inoculation (immunity test)*: 254 days after the first inoculation and 104 days after complete recovery, he again was injected parenterally with the serum hepatitis agent (plasma A, 5 ml.). From the 38th to the 112th day after this injection, he had intermittent vague symptoms and/or laboratory findings suggestive of mild hepatic disturbance. The symptoms were mild and occurred intermittently in episodes of 24 to 48 hours duration. They included vague muscle pain, slight anorexia, mild nausea, excessive belching, vague abdominal discomfort and general malaise. The symptoms never were incapacitating. The laboratory findings included intermittently positive tests for urine bilirubin and elevation

of sedimentation rate without other obvious explanation. (3) *Third inoculation (cross-immunity test)*: 190 days after the second inoculation and 78 days after recovery, he was injected parenterally with the agent of infectious hepatitis (serum pool 2 SIH, 2 ml.). On the 35th day after his inoculation, he developed fever (100.2° F. oral), malaise, weakness, easy fatigue, joint, muscle, and back pain, headache, mild anorexia, excessive belching and abdominal discomfort. Some of these symptoms persisted intermittently until the 54th day. During this period, cephalin cholesterol flocculation tests gave significantly positive reactions but the other liver function studies showed no significant abnormalities.

## J. C.

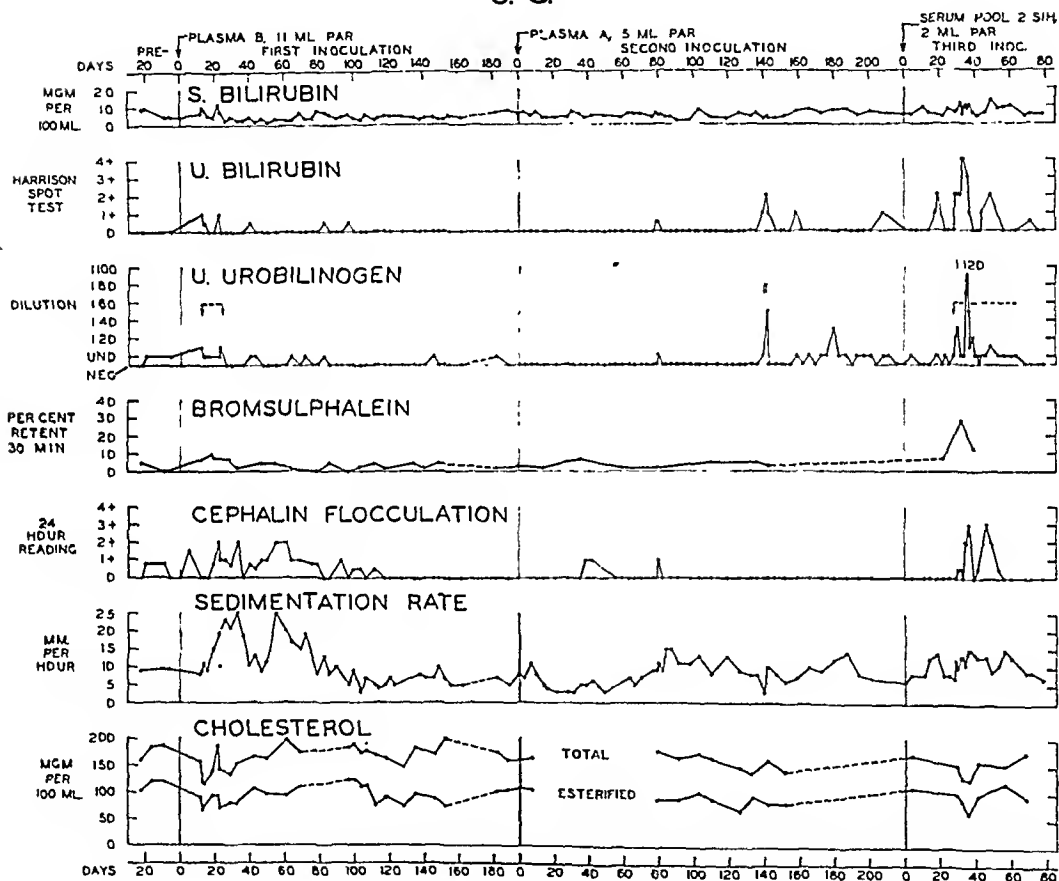


FIG. 4.—Laboratory and other data on subject J. C. (See legends of Figs. 1 and 3.)

*Subject H. J. C.* (Fig. 6.) As previously mentioned, this volunteer had naturally occurring catarrhal jaundice (probably infectious hepatitis) in 1939. (1) *First inoculation* (1943): on the 61st day after parenteral injection with the agent of serum hepatitis (yellow fever vaccine, 2 ml.) he developed hepatitis without jaundice. (2) *Second inoculation (immunity test)*: 226 days after the first inoculation and 125 days after recovery, he again was injected parenterally with the serum hepatitis agent (plasma A, 5 ml.). During the subsequent 218 days, he had no definite symptoms although abnormalities in the results of the cephalin cholesterol flocculation test and the Harrison spot test for urine bilirubin were suggestive of subclinical hepatic disturbance. (3) *Third inoculation (cross-immunity)*: 218 days after the second inoculation he was injected parenterally with the agent of infectious hepatitis (serum pool



2 SIH, 2 ml.). During the 125 days which have elapsed to date, he has had no characteristic symptoms or laboratory evidences of hepatic disturbance.

**Controls.** The 3 normal controls inoculated parenterally with the serum hepatitis agent (plasma A, 5 ml.) at the time of the immunity tests all developed hepatitis with jaundice after 102, 103 and 108 days. Five of the 6 normal controls inoculated parenterally with this agent (plasma A; doses ranging from 1 to 250 ml.) at other times developed hepatitis with overt jaundice after 60 to 110 days (the one who failed to develop the disease received 100 ml. of plasma A).

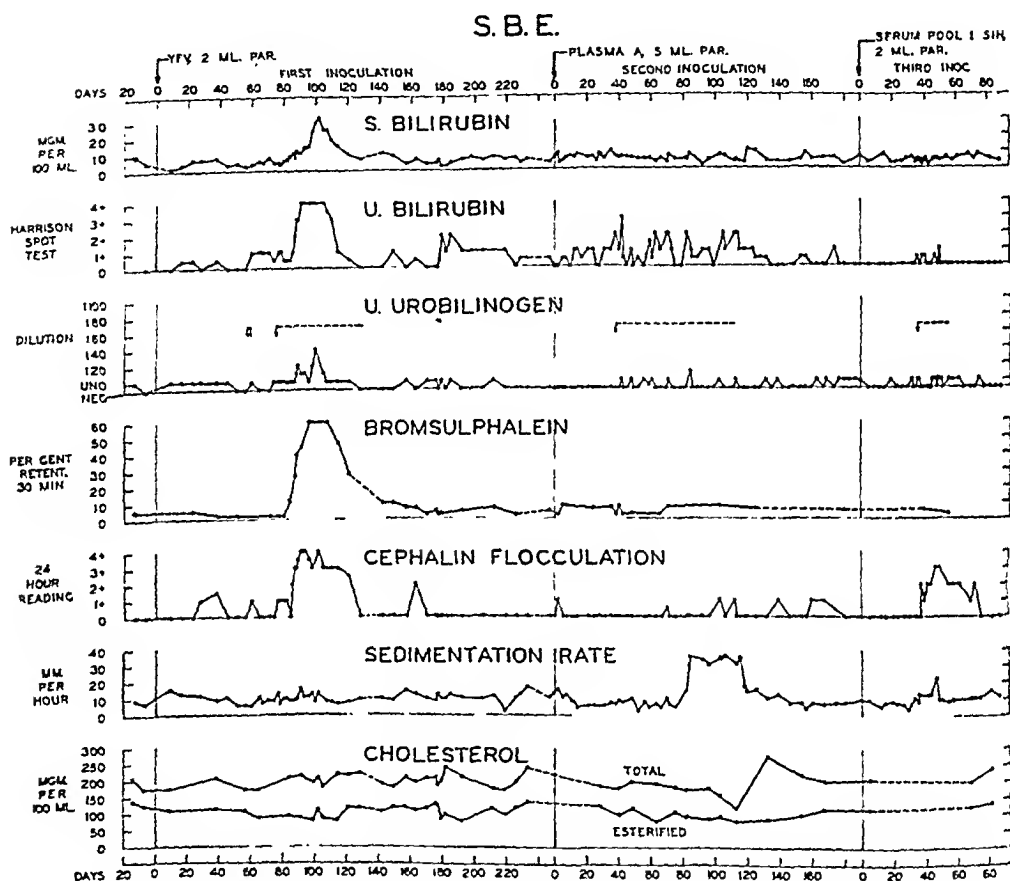


FIG. 5.—Laboratory and other data on subject S. B. E. (See Fig. 1 for legend.) The information available strongly suggests that the yellow fever vaccine and plasma A contained the same causative agent of homologous serum hepatitis (see text).

At the same time that 5 of the 6 men in the cross-immunity test group were inoculated parenterally with the agent of infectious hepatitis (serum pool 2 SIH, 2 ml.), 6 normal controls also were inoculated with this agent, 3 subjects receiving 2 ml. of serum pool 2 SIH parenterally and 3 receiving 3 ml. of this serum pool orally. None of the 3 controls inoculated parenterally has developed hepatitis during the 180 days elapsing to date whereas 2 of the 3 inoculated orally developed hepatitis with jaundice after incubation periods of 26 and 33 days. Similar results were obtained on oral and parenteral administration to normal controls of a Seitz filtrate of feces pool 1 FIH, which contained the same agent of infectious hepatitis as serum pool 2 SIH.<sup>13</sup> None of the 3 inoculated parenterally with the Seitz filtrate has developed hepatitis in the 180 days which have elapsed whereas all of the 3 inoculated

orally developed hepatitis with jaundice after incubation periods of 28, 30 and 32 days. Thus 5 of the 6 normal controls inoculated *orally* with materials containing this agent of infectious hepatitis developed the disease in contrast to none of the 6 inoculated *parenterally* with the same materials.

## H. J. C.

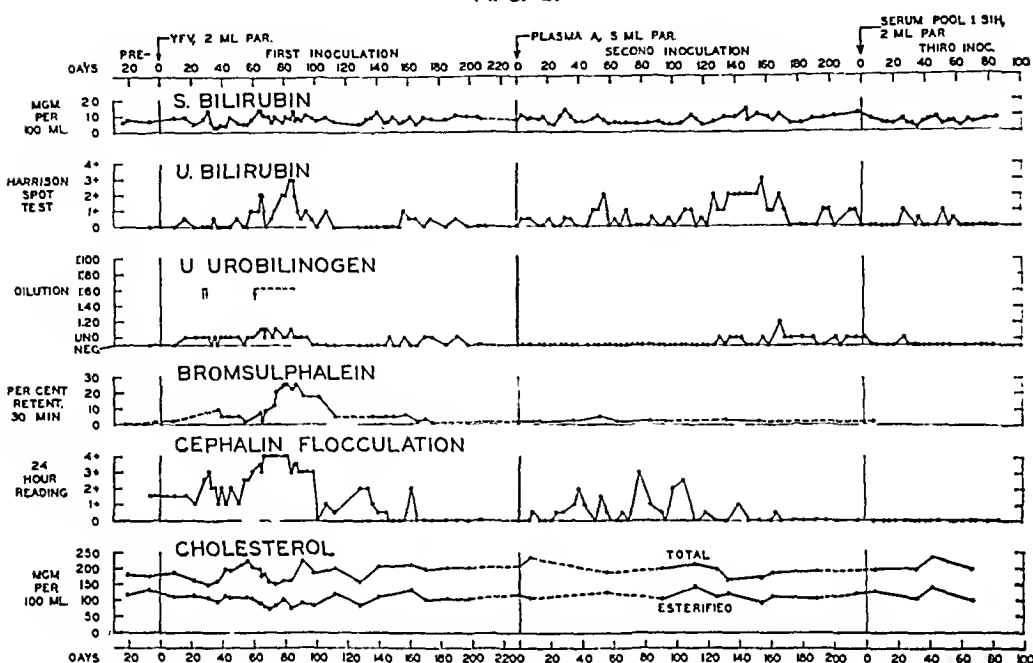


FIG. 6.—Laboratory and other data on subject H. J. C. (See legends of Figs. 1 and 5.) This subject had naturally occurring infectious hepatitis in 1939, 4 years prior to the first experimental inoculation.

**Clinical Observations.** In 11 of the 13 men (test group and controls) who developed hepatitis after inoculation with the serum hepatitis agent, the acute onset occurred after 60 or more days and none of the 13 men had elevations of temperature above 100° F. (oral). After oral or parenteral inoculation with the agent of infectious hepatitis, the longest incubation period in the 10 men (5 of the test group, 5 orally inoculated controls) contracting the disease was 37 days and all had elevations of oral temperature exceeding 100° F. at the onset.

**Discussion.** None of the 6 men who were inoculated with a causative agent of homologous serum hepatitis after recovery from homologous serum hepatitis developed incapacitating symptoms or jaundice. Although mild symptoms and/or laboratory findings suggestive of transient hepatic disturbance were observed in 5 of the 6 men, these manifestations were clinically insignificant and were not sufficient to establish definitely a diagnosis of hepatitis. On the other hand, 8 of the 9 normal controls inoculated with the same agent developed hepatitis with overt jaundice. Compared to the control subjects it is apparent that the men who previously had had homologous serum hepatitis were resistant to this causative agent of serum hepatitis.

The finding that the 6 men of the test group were resistant to the serum hepatitis agent in plasma A supports the presumption that

plasma A, plasma B and the yellow fever vaccine (see Material and Methods) contained the same hepatitis agent. The demonstration of resistance (immunity)\* to the serum hepatitis agent also supports the diagnosis of the initial non-icteric illnesses of N. H. H., J. C. and H. J. C. as hepatitis without jaundice. The high susceptibility of the men in the control group to the serum hepatitis agent in plasma A provides evidence that the resistance of the test group to this agent resulted from their previous attacks of homologous serum hepatitis. For this reason the acquired resistance of N. H. H. and J. C. probably can be regarded as an illustration of the production of immunity by mild infection, which under ordinary circumstances, would not have been recognized as hepatitis.

Although resistant to the serum hepatitis agent, 5 of the 6 men again developed hepatitis after oral (1 man) or parenteral (5 men) inoculation with materials containing the causative agent of infectious hepatitis. Of the 5 men inoculated *parenterally* with such material, only 1 (H. J. C.) showed no subsequent evidence of hepatitis and he previously had had both infectious and homologous serum hepatitis. This is of importance because none of the 6 normal controls injected *parenterally* with this causative agent of infectious hepatitis developed the disease, a result which raises the question as to whether the hepatitis occurring in those who previously had had serum hepatitis was due to the agent of infectious hepatitis or to a reactivation of the serum hepatitis agent. Although reactivation of the serum hepatitis agent cannot be completely excluded, the following observations make this explanation improbable: (1) reactivation did not occur in Oliphant's series of inoculations 12 to 18 months after an attack of homologous serum hepatitis;<sup>14</sup> (2) the onset of hepatitis occurred 28 to 37 days after the inoculation, an interval corresponding to the incubation period of infectious hepatitis; (3) the subjects had been shown to be resistant to the agent of serum hepatitis and disappearance of this resistance during the interval between the immunity and cross-immunity tests seems improbable for the following reasons: (a) Oliphant's study of immunity<sup>9</sup> following homologous serum hepatitis indicated that the immunity persisted for at least 12 to 18 months. In the present investigation, the cross-immunity tests were completed within 12 months after the original attack of homologous serum hepatitis. Furthermore, during that 12 months, the men again had been inoculated with a serum hepatitis agent, a procedure which not only demonstrated their resistance to that agent but also might have maintained or even increased that resistance. (b) The only one of the test group who failed to show some evidence of hepatitis after inoculation with material containing the agent of infectious hepatitis previously had had both homologous serum hepatitis and infectious hepatitis, suggesting that he was protected by the previous attack of infectious hepatitis. The possibility that the serum hepatitis and infectious hepatitis agents were the same and that the last attacks of hepatitis

\* The term "immunity" is used broadly throughout this report to indicate either complete or almost complete resistance to the hepatitis agent used.

were due to an overwhelming dose, sufficient to overcome the previously demonstrated resistance to the serum hepatitis agent, probably can be eliminated by the failure of the normal controls (injected parenterally) to develop the disease. The foregoing observations seem to justify the conclusion that the hepatitis which occurred in the men of the test group, following inoculation with materials containing the causative agent of infectious hepatitis, was not due to reactivation of the serum hepatitis agent, to reinfection with that agent after disappearance of the previously demonstrated resistance, or to breakdown of that resistance by an overwhelming dose of the same agent. For these reasons, it is probable that the last attacks of hepatitis in the men of the test group were due to the causative agent of infectious hepatitis which was known to be present in the serum with which they were inoculated (cross-immunity test). Thus it appears that these men were not protected against the agent of infectious hepatitis by their resistance to the agent of homologous serum hepatitis. The results strongly suggest a difference in the antigenic properties of the two agents employed. The difference may be explained either, on the basis of antigenic variation in strain of a single type of virus agent or on the basis of two different types of virus agent. Additional information may be provided by the challenge of volunteers shown to be immune to the causative agent of infectious hepatitis with the serum hepatitis agent, the reverse of the procedure employed in the present study. This type of cross immunity study will be conducted if volunteers continue to be available.

The experimentally induced infectious hepatitis in all cases was characterized by elevations of temperature greater than 100° F. at the onset and by an incubation period that did not exceed 37 days regardless of the route of inoculation (parenteral or oral). The experimentally induced homologous serum hepatitis was characterized by an interval of 60 or more days between inoculation and jaundice in 9 of the 11 cases and no elevations of temperature above 100° F. (oral) were observed. Although exceptions to the characteristic pattern have been noted, these differences are in accord with those described in the literature and they provide support for the immunologic evidence indicating some difference between the causative agents of the two types of hepatitis.

A difference in the causative agents employed herein also is suggested by the variation in results with different routes of inoculation. Thus *oral* administration of this agent of infectious hepatitis produced the disease in 5 of 6 normal persons whereas *parenteral* administration of the same agent failed to produce the disease in any of 6 other normal persons. On the other hand, *oral* administration of materials (plasma and feces) from patients with homologous serum hepatitis to a small group of normal persons has failed to induce the disease,<sup>13</sup> whereas *parenteral* administration of this serum hepatitis agent produced the disease in 8 of 9 normal persons. The experimental results with this causative agent of infectious hepatitis have suggested that normal persons are much more apt to develop the disease when the

agent is administered orally than when it is injected parenterally. In respect to this agent of homologous serum hepatitis, the preliminary studies have suggested that it is more apt to induce the disease in normal persons when injected parenterally than when administered orally. The results of additional experiments now in progress may confirm or modify these preliminary impressions.

The data also suggest that the ability of this causative agent of infectious hepatitis to induce the disease when injected parenterally may depend, in part, on previous infection by the serum hepatitis agent. Of the 10 persons without previous history of infectious hepatitis who were injected parenterally with this agent of infectious hepatitis, only the 4 who previously had had homologous serum hepatitis developed the disease. This strongly suggests that the persons who previously had had homologous serum hepatitis were more susceptible to the parenterally injected agent of infectious hepatitis than the controls with no previous history of homologous serum hepatitis.

**Summary and Conclusions.** Homologous serum hepatitis was induced experimentally in 6 human volunteers by the parenteral administration of materials known to contain a causative agent of this disease. After recovery, the 6 men were inoculated parenterally with a plasma that contained a causative agent of homologous serum hepatitis in order to test for homologous immunity. Nine normal control subjects without previous history of hepatitis also were inoculated parenterally with the same plasma. None of the 6 men in the test group developed incapacitating symptoms or jaundice, whereas 8 of the 9 controls developed hepatitis with jaundice.

The 6 men then were inoculated (1 orally, 5 parenterally) with materials known to contain a causative agent of infectious (epidemic) hepatitis in order to test for cross-immunity. Twelve normal controls without previous history of hepatitis also were inoculated with these materials, 6 receiving the infectious material orally and 6 receiving it parenterally. Of the 6 men tested for cross-immunity, 5 again developed hepatitis, the evidence being conclusive in 4 and very suggestive in the fifth person. The one who showed no evidence of hepatitis previously had had both infectious hepatitis and homologous serum hepatitis. None of the 6 normal controls inoculated parenterally developed hepatitis, whereas 5 of the 6 normal controls inoculated orally contracted typical infectious hepatitis.

The interval between inoculations with serum hepatitis agent and the onset of jaundice usually exceeded 60 days, whereas that between inoculation with the agent of infectious hepatitis and the onset of this disease did not exceed 37 days regardless of the route of inoculation. Oral temperatures did not exceed 100° F. in the cases due to the serum hepatitis agent, whereas the oral temperature exceeded 100° F., regardless of the route of inoculation, in all of the cases due to the agent of infectious hepatitis.

The groups employed in the studies reported herein are too small to warrant final conclusions regarding the relationship of the causative agents of infectious hepatitis and homologous serum hepatitis. Never-

theless the following observations provided considerable evidence that the two agents employed were not identical: (1) The susceptibility to the causative agent of infectious hepatitis of volunteers previously shown to be resistant to the causative agent of homologous serum hepatitis, suggesting a lack of cross-immunity, presumably due to a difference in the antigenic properties of the two agents. (2) The apparent difference in the ability of the two agents to produce hepatitis in normal persons when injected parenterally as indicated by (a) the occurrence of hepatitis in 8 of 9 normal persons who received the serum hepatitis agent parenterally, and (b) the failure of hepatitis to occur in any of 6 normal persons injected parenterally with the same causative agent of infectious hepatitis that produced the disease in 5 of 6 normal persons who received it orally.

**Addendum.** Since the preparation of this report for publication, Havens has reported an experimental study of immunity in hepatitis (Havens, W. P., Jr.: Experiment in Cross Immunity Between Infectious Hepatitis and Homologous Serum Jaundice, *Proc. Soc. Exp. Biol. and Med.*, 59, 148, 1945). Three men who had recovered from experimentally induced homologous serum hepatitis were inoculated parenterally with an agent of infectious hepatitis. All developed hepatitis after incubation periods of 20 to 25 days. However, the existence of homologous immunity to the causative agent of homologous serum hepatitis was not determined in these men or in suitable controls so that no definite conclusions regarding cross immunity were drawn.

Since submission of this report for publication, 8 volunteers have been found to be resistant to reinfection by a causative agent of infectious (epidemic) hepatitis up to at least 8 months after recovery from previous hepatitis due to the same agent. Thus experimental evidence indicating the existence of homologous immunity following both infectious hepatitis and homologous serum hepatitis now is available. For this reason the susceptibility to the agent of infectious hepatitis of volunteers shown to be resistant to the agent of homologous serum hepatitis is best explained by a lack of cross immunity and by a difference, at least in their antigenic properties, in the two hepatitis agents studied.

This investigation was made possible by the cooperation of the administrative staffs of Selective Service (Camp Operations Division), the National Service Board for Religious Objectors, the American Friends Service Committee, the Philadelphia State Hospital, the New Jersey State Hospital, and we are particularly indebted to the members of Civilian Public Service Unit No. 140, Philadelphia, Penna., who volunteered as subjects in these investigations. The biochemical studies were supervised by Dr. John G. Reinhold, Principal Biochemist of the Philadelphia General Hospital.

#### REFERENCES

1. CAMERON, J. D. S.: *Quart. J. Med.*, 12, 139, 1943.
2. DIBLE, J. H., McMICHAEL, J., and SHERLOCK, S. P. V.: *Lancet*, 2, 402, 1943.
3. FINDLAY, G. M., MARTIN, N. H., and MITCHELL, J. B.: *Lancet*, 2, 365, 1944.
4. GELLIS, S. S., STOKES, J., JR., BROTHER, G. M., HALL, W. A., GILMORE, H. R., and BEYER, E.: *J. Am. Med. Assn.*, 128, 1062, 1945.
5. HAVENS, W. P., JR.: *Proc. Soc. Exp. Biol. and Med.*, 58, 203, 1945.
6. LUCKE, B.: *Am. J. Path.*, 20, 471, 1944.
7. McFARLAN, A. M., and CHESNEY, G.: *Lancet*, 1, 816, 1944.
8. McGUINNESS, A.: Personal communication.
9. NEEFE, J. R., MILLER, T. G., and CHORNOCK, F. W.: *AM. J. MED. SCI.*, 207, 626, 1944.
10. NEEFE, J. R., STOKES, J., JR., REINHOLD, J. G., and LUKENS, F. D. W.: *J. Clin. Invest.*, 23, S36, 1944.
11. NEEFE, J. R., STOKES, J., JR., and REINHOLD, J. G.: *AM. J. MED. SCI.*, 210, 29, 1945.
12. NEEFE, J. R., and STOKES, J., JR.: *J. Am. Med. Assn.*, 128, 1063, 1945.
13. NEEFE, J. R., and STOKES, J., JR.: Unpublished data.
14. OLIPHANT, J. W.: *Pub. Health Rep.*, 59, 1614, 1944.
15. STOKES, J., JR., and NEEFE, J. R.: *J. Am. Med. Assn.*, 127, 144, 1945.
16. WITTS, L. J.: *Brit. Med. J.*, 1, 4352, 1944.

# STREPTOMYCIN: ABSORPTION, DIFFUSION, EXCRETION AND TOXICITY\*

By DOROTHY H. HEILMAN, M.D.

DIVISION OF CLINICAL PATHOLOGY

FORDYCE R. HEILMAN, M.D.

SECTION ON BACTERIOLOGY

H. CORWIN HINSHAW, M.D.

DONALD R. NICHOLS, M.D.

AND

WALLACE E. HERRELL, M.D.

DIVISION OF MEDICINE, MAYO CLINIC  
ROCHESTER, MINNESOTA.

THE antibiotic agent streptomycin was described by Schatz, Bugie and Waksman.<sup>8</sup> Several reports<sup>1,3,4-7,10,11</sup> have appeared which indicate that this substance may prove of value in treatment of infections caused by certain gram-negative, gram-positive and acid-fast bacteria. At the Mayo Clinic studies were begun in September, 1944, to explore the possible methods of administration and to obtain some information concerning absorption, diffusion, excretion and toxicity of the substance.

Streptomycin has been administered to human subjects by the continuous intravenous, intermittent intravenous, intermittent intramuscular, continuous intramuscular and intermittent subcutaneous routes. Streptomycin also has been administered intrathecally, by means of nebulization and orally. For determination of the concentration of streptomycin in various body fluids two methods have been employed. One method used was a modification of the Fleming slide cell technique described by one of us (D. H. H.).<sup>2</sup> The other method employed was a modification of the cup plate method of assay.<sup>9</sup> The test organism used in the cup plate method in determining concentration of streptomycin in the blood serum was a sensitive strain of *Staphylococcus aureus*. For determinations of the concentration of streptomycin in the urine, the test organism used was *Bacillus subtilis*. The present report deals with the results obtained in the studies just mentioned.

**Absorption Following Various Methods of Administration.** *Continuous Intravenous Drip.* On a theoretic basis, the continuous intravenous drip method of administration, which often has been used for administration of penicillin, appears to be the most satisfactory method of maintaining constant concentrations in the blood of patients who are

\* The streptomycin used in these studies was kindly supplied, for the most part, by Dr. D. F. Robertson of Merck & Co., Inc. Small supplies of streptomycin also have been furnished by Abbott Laboratories, The Upjohn Company and Parke, Davis & Co. Some streptomycin, furthermore, was furnished by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for experimental investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

receiving streptomycin. Patients have received as much as 4,000,000 units of streptomycin per day by this method. The unit of potency, as originally described by the investigators at Rutgers University, was that quantity of the dry material which would inhibit the growth of a given strain of *Escherichia coli* in 1 cc. of nutrient broth or agar. It has been observed that the blood of a patient who was receiving 2,000,000 units of streptomycin per 24 hours by the intravenous drip method contained 31 units of streptomycin per cc., according to determinations made by the cup plate method. Likewise, the blood of a single patient who was receiving 1,000,000 units of streptomycin per 24 hours by this method contained between 6 and 8.7 units of streptomycin per cc.

Venous irritation at the site of injection has occurred at times; however, actual thrombosis rarely has been associated with this method of administration. Streptomycin of high potency is not seriously irritating for subcutaneous tissues and, therefore, significant discomfort will not result if the needle is accidentally displaced and the solution is forced into the subcutaneous tissues.

*Intermittent Intravenous Administration.* Although streptomycin may be administered intermittently by the intravenous route, intravenous administration has no advantages over intramuscular or subcutaneous injection. The concentration in the blood following a single intravenous injection is high for a short period but falls off more rapidly than when any other means of intermittent administration has been utilized (Tables 1 and 2). Discomfort has not occurred when as much as 100,000 to 200,000 units of streptomycin has been given in 10 to 20 cc. of physiologic saline solution. Single or repeated injections every 3 hours have been carried out by this method.

TABLE 1.—CONCENTRATIONS OF STREPTOMYCIN IN BLOOD SERUM FOLLOWING REPEATED INJECTIONS

Administration of streptomycin				Streptomycin in blood serum (units* per cc.)					Method of assay	Reactions
Case	Route	Dose every 3 hr. (units)	No. doses	Hours after first dose						
				1	3	6	9	12		
1	I.V.†	100,000	3	3 5.4	1.5 2.9	3 4.5	3 3.4	1.5 2.3	Slide cell Cup plate	None
2	I.V.	100,000	3	3 4.6	1.5 3	1.5 4	1.5 5.4	1.5 2.8	Slide cell Cup plate	None
3	I.M.†	100,000	3	1.5 2.7	1.5 2.6	1.5 2.6	1.5 3.3	0 1.2	Slide cell Cup plate	None
4	I.M.	100,000	3	1.5 3	1.5 3.3	3 4.5	3 4.3	1.5 2.8	Slide cell Cup plate	None
5	I.M.	400,000	3	3 3.6	3 2.1	6 11	3 3.9	3 2.3	Slide cell Cup plate	None
6	I.M.	400,000	3	3 5.7	3 2.8	3 5.8	3 6.9	0 2.6	Slide cell Cup plate	None
7	I.V.	400,000	3	14.5	14.9	13.2	7.5	4.1	Cup plate	Joint pain, fever, nausea, albuminuria, hematuria

\* The units of potency used in these studies have been described elsewhere. Suffice to say here that the values obtained with their use were substantially equivalent to those obtained with the originally described *Escherichia coli* unit of the Rutgers investigators.

† I.V. = intravenous; I.M. = intramuscular.



TABLE 2.—CONCENTRATIONS OF STREPTOMYCIN IN BLOOD SERUM FOLLOWING SINGLE OR INTERMITTENT INJECTIONS

Case	Route of admin.	Amount per dose (units)	Streptomycin in blood serum (units per cc.)					Method of assay
			Hours after injection					
			½	1	2	3	4	
1	I.V.	100,000	6	6	3	0	..	Slide cell
2	I.M.	100,000	3	3	3	3	..	Slide cell
3	Subcut.	100,000	3	3	3	1.5	..	Slide cell
4	Subcut.	200,000	6 8.8	6 8.8	6 7.2	6 6.2	.. ..	Slide cell Cup plate
5	Subcut.	200,000	12.5 10	6 7.7	6 6	3 ..	.. ..	Slide cell Cup plate
6	Subcut.	200,000	12.5	25	6	6	..	Slide cell
7	Subcut.	100,000*	..	12.5	..	..	..	Slide cell
8	Subcut.	100,000*	..	12.5	25	6	..	Slide cell
9	Subcut.	115,000*	..	12.5	..	..	..	Slide cell
10	Subcut.	115,000*	..	6	..	..	..	Slide cell
11	Subcut.	150,000*	..	12.5 16.6	.. ..	.. ..	.. ..	Slide cell Cup plate
12	Subcut.	250,000*	..	25 31	25 24	25 16	25 10	Slide cell Cup plate

\* Dose indicated was administered every 3 hours.

*Intermittent Intramuscular Administration.* Under most clinical circumstances, probably intramuscular administration is the method of choice at present. Reasonable concentrations are maintained in the blood for at least 3 hours after administration, by this method, of adequate doses of streptomycin. In some instances, antibacterial amounts of streptomycin will be found to remain in the blood for as long as 4 to 6 hours after the last intramuscular injection has been made. For this method of administration the volume of solution which contains the streptomycin is kept at a minimum. Streptomycin of high potency can be administered by intramuscular injection; for instance, 100,000 units can be administered in 1 cc. of physiologic saline solution. The concentration of streptomycin in the blood following single and repeated intramuscular injections is recorded in parts of Tables 1 and 2. Intermittent intramuscular injection is made either into the gluteal or the deltoid muscles. A standard 22 gauge needle  $2\frac{1}{2}$  inches (about 6.5 cm.) in length, usually is employed for making the injections.

*Continuous Intramuscular Administration.* A convenient method for continuous intramuscular administration of streptomycin is as follows: The contemplated daily dose of streptomycin is dissolved in 1 liter of saline solution and the intramuscular injection is made with the standard intramuscular needle. The rate of flow is regulated at approximately 8 to 10 drops per minute.

*Intermittent Subcutaneous Administration.* The subcutaneous method at times may prove satisfactory for repeated injections of streptomycin. Preparations of highest potency can be injected subcutaneously

every 3 hours, probably with less discomfort than when any other route of administration is used. Subcutaneous administration of relatively crude preparations at times may produce some pain and local irritation at the site of injection. Reasonably antibacterial amounts of streptomycin have been maintained in the blood of patients who have received streptomycin in amounts of 100,000 units every 3 hours subcutaneously (Table 2). One advantage of the subcutaneous method of administration is that highly trained personnel are not required. Student nurses as well as others can administer the material in this fashion. From limited studies it also appears that fairly purified streptomycin is less irritating than is penicillin to the subcutaneous tissues.

*Intrathecal Administration.* For reasons which will be mentioned later in connection with the diffusion of streptomycin, at times it may be necessary to administer the drug by the intrathecal route. Single injections of as much as 100,000 units of streptomycin, dissolved in 10 cc. of physiologic saline solution, have been administered intrathecally for meningitis. No evidence of serious untoward reactions has appeared. Antibacterial amounts of the substance have been found in the cerebrospinal fluid for at least 24 hours after these injections (Table 3). In 1 instance, detectable amounts of the substance were present in the cerebrospinal fluid for a considerably longer time.

TABLE 3.—STREPTOMYCIN IN CEREbroSPINAL FLUID

Case	Route of admin.	Dose (units)	Doses per day	Concentration in blood serum (units per cc.)				Concentration in cerebrospinal fluid (units per cc.)			
				Hours after injection				Hours after injection			
				½	1	2	3	2	3	12	26
1	Intrathecal	50,000 100,000	1 1	..	..	..	..	..	..	50 6	6
2	Subcut.	50,000	8	..	..	..	..	None detectable			
3	I.M.	60,000	8	..	1.5	1.5	1.5	0	0		
4	I.M.	60,000	8	..	3	3	1.5	0	0		
5	Subcut.	200,000	1	12.5	6	6	3	0	0		
6	Subcut.	200,000	1	6	6	6	6	0	0		

*Administration by Nebulization.* Experimentally, streptomycin in concentrations as high as 50,000 units per cc. was found to produce no irritation of the mucosa of the tracheobronchial tree. Three patients concerned in the present study received streptomycin by the tracheobronchial route. The material was administered by means of a nebulizer\* connected to an oxygen tank equipped with reducing valve and flowmeter. As much as 500,000 units per day has been given, without interruption for periods as long as 4 weeks, for tuberculous involvement of the larynx and tracheobronchial tree. During the period of treatment, streptomycin was not demonstrable in the blood serum of the patients and excretion of streptomycin in the urine was negligible. In only 1 instance could streptomycin be detected in the urine of a patient who was receiving the agent by nebulization. This patient

\* Vapo-efrin nebulizer.

was able to hold her breath for 5 seconds at the time of each inspiration, and she received 500,000 units of streptomycin in a period of 24 hours. The 24 hour urine specimen was found to contain 30,000 units of streptomycin. As was true of the other patients to whom the agent was administered by this method, streptomycin could not be detected in the blood serum.

*Oral Administration.* In connection with certain studies on the intestinal bacterial flora, a limited number of patients were given streptomycin by the oral route. One of us (F. R. H.) has found that striking reduction in the number of *E. coli*, as well as of other organisms present in the fecal stream, occurs when patients receive streptomycin orally. Studies indicate that streptomycin cannot be demonstrated in the blood serum when patients receive as much as 500,000 units of streptomycin per day by mouth. The substance was administered in doses of 125,000 units every 6 hours. Likewise, excretion of streptomycin in the urine of 1 such patient was negligible in a period of 24 hours. It appears, therefore, that streptomycin is not absorbed from the bowel when it is given in the manner described and when the total daily dose does not exceed that named. Knowledge of whether or not absorption will occur following administration of larger doses of streptomycin must await further studies.

*Diffusion and Excretion. Diffusion Into Cerebrospinal Fluid.* It was considered of importance to determine whether or not diffusion of streptomycin into the cerebrospinal fluid takes place. Intramuscular and subcutaneous injections of varying amounts of streptomycin have been administered to human beings. The largest single dose administered in this study was 200,000 units. Concentrations in the blood serum and in the cerebrospinal fluid were determined at various intervals following the injections. In some cases, determinations were carried out on blood serum collected  $\frac{1}{2}$ , 1, 2 and 3 hours after the injection. It is evident, from examination of the data given in Table 3, that antibacterial amounts were present in the blood of these patients during this entire period. Detectable amounts of streptomycin were not found in cerebrospinal fluid removed 2 and 3 hours after injection. It would appear, therefore, that diffusion of streptomycin into the cerebrospinal fluid, when given in the amounts stated, does not take place readily. On the other hand, large doses given intramuscularly, subcutaneously or intravenously, in the presence of meningitis, have resulted in diffusion into the cerebrospinal fluid, to yield concentrations therein approximating one-fifth that in the blood serum of the same patients.

*Diffusion Through the Placenta (Placental Transmission).* It was considered desirable to determine whether or not streptomycin, when present in the blood of the mother; passed the placental barrier and was, therefore, present in the fetal circulation. In this study varying amounts of streptomycin were administered before the time of delivery. The interval of time between the last dose and the time of delivery varied from 45 minutes to 2 hours and 35 minutes. In some instances,

single injections of streptomycin were carried out and in some instances it was possible to give repeated injections before the time of delivery. Blood was obtained from the mother at the time of delivery and specimens of blood from the umbilical cord were obtained simultaneously. It is evident, from examination of Table 4, that streptomycin traverses the placenta and is readily available in the fetal circulation. The concentration of streptomycin in the blood of the umbilical cord appears to vary somewhat, depending on the dose and the time which elapses between the last injection and birth.

TABLE 4.—PLACENTAL TRANSMISSION OF STREPTOMYCIN

Case	Route of admin.	Dose (units)	No. doses	Delivery (time after dose)	Concentration in blood (units per cc.)		Method of assay
					Maternal	Cord	
1	Subcut.	100,000	1	1 hr. 30 min.	6.0	1.5	Slide cell
2	Subcut.	100,000	1	2 hr. 35 min.	3.0	3.0	Slide cell
3	Subcut.	100,000	7*	45 min.	12.5	12.5	Slide cell
4	Subcut.	100,000	7*	1 hr. 30 min.	6.0 10.5	6.0 6.4	Slide cell Cup plate

\* Administered every 2 hours.

*Excretion of Streptomycin in Bile.* Studies on the excretion of streptomycin in bile are incomplete but are sufficient to indicate that the material apparently is concentrated and excreted in the bile. The results of observations on excretion of streptomycin in bile are shown in Table 5. The patient received 100,000 units of streptomycin subcutaneously every 3 hours for 5 days. Two hours after the first injection of 100,000 units of streptomycin, the blood serum contained 6 units of streptomycin per cc. At this time, the concentration of streptomycin in the bile was 12.5 units per cc. The concentrations in the bile, on the 2nd and 3rd days of administration of streptomycin, were between 3 and 6 units of streptomycin per cc.

TABLE 5.—EXCRETION OF STREPTOMYCIN IN BILE\*

Administration of streptomycin			Day	Hour after first dose	Concentration in blood serum (units per cc.)	Concentration in bile (units per cc.)	Total 24-hr. output in bile (units)
Route	Dose every 3 hr. (units)	Doses per day					
Subcut.	100,000	8	1	2 4	6 6	12.5 12.5	
Subcut.	100,000	8	2	..	..	6	2010
Subcut.	100,000	8	3	..	..	3	960

\* Determinations of streptomycin in the bile were made by means of the slide cell method of assay

Determination of the quantity of bile and of bile salts excreted in 24 hours is said to be a reliable test of liver function. It is evident, from examination of Table 6, that no serious alteration occurred in either of these values during the period when the patient just referred to was receiving 800,000 units of streptomycin per 24 hours. It should be emphasized that these data do not permit conclusions as to

the possible effect of streptomycin on liver function following long periods of administration of the preparation.

TABLE 6.—EFFECT OF STREPTOMYCIN ON VOLUME OF BILE AND WEIGHT OF BILE SALTS EXCRETED\*

Day	Dose of streptomycin per 24 hr. (units)	Bile (cc.)	Bile salts per 24 hr., (gm.)
1 . . . . .	800,000	250	11.25
2 . . . . .	800,000	250	11.68
3 . . . . .	800,000	285	9.69
4 . . . . .	800,000	255	9.51
5 . . . . .	800,000	315	11.84

\* This is the same case as that represented in Table 5.

*Excretion of Streptomycin in Urine.* It is evident that following systemic administration of streptomycin, fairly large amounts of the material are absorbed into the general circulation and excreted in the urine. From one-half to three-fourths of the total amount of streptomycin administered is usually excreted in the urine during the 1st 24 hours. High concentrations (as much as 434 units per cc.) may on occasion be found in the urine of patients who have received large amounts of the material (Table 7). It should be emphasized here that the cup plate method is the technique of choice for determining the presence of streptomycin in the urine.

TABLE 7.—URINARY EXCRETION OF STREPTOMYCIN\*

Case	Route of admin.	Dose every 3 hr. (units)	Doses	Urine	Streptomycin (units per cc. of urine)	Total urine excreted (cc.)	% streptomycin excreted
1	I.V.	100,000	3	1st 24 hr.	120	2000	80.0
2	I.V.	100,000	3	1st 24 hr.	126	1245	52.3
3	I.M.	100,000	3	1st 24 hr. 2nd 24 hr.	104 7.2	1665 725	57.4 1.7
4	I.M.	100,000	3	1st 24 hr. 2nd 24 hr.	78.4 5.6	2510 1350	65.6 2.5
5	I.M.	400,000	3	1st 24 hr. 2nd 24 hr.	137 8.1	1850 2150	21.1 1.1
6	I.M.	400,000	3	1st 24 hr.	137	1460	16.7
7	I.V.	400,000	3	1st 24 hr.	434	1740	62.9

\* The cup plate method of assay was used. These are the same 7 cases as those represented in Table 1.

*Consideration of Toxicity. Irritation at the Site of Injection.* It has been pointed out that local irritation may occur occasionally following administration of streptomycin by the intravenous drip method. Actual thrombosis rarely has occurred; however, often it is necessary to change the site of injection frequently. Pain at the site of subcutaneous or intramuscular injection also may occur, especially when streptomycin of low potency is used. The discomfort is described as a burning sensation and usually is of short duration. Neither of these reactions has been troublesome, nor do the reactions seriously interfere with administration of the agent. It is exceedingly important

that the size of the inoculum be kept as small as possible (no more than 2 or 3 cc.).

*Chills and Fever.* On occasions, chills and fever have occurred following administration of streptomycin. This reaction is not unlike reactions encountered in the past in connection with administration of penicillin which was not pyrogen-free. More frequently a slight elevation of temperature is noted, which is usually not of serious significance.

*Cutaneous Toxic Manifestations.* At times generalized flushing, not unlike that seen in association with a histamine reaction, has been observed in cases in which relatively impure streptomycin has been administered. Likewise, dermatitis (toxic erythema) and cutaneous eruptions of an urticarial type have occurred following administration of streptomycin as it is available at present for clinical use. Although administration of streptomycin may be continued in the presence of these cutaneous eruptions, it is exceedingly important to remember that severe dermatitis may result.

*Joint Pain.* Several patients who received streptomycin complained of severe pain in the joints and muscles of the extremities. Such patients usually exhibited fever and other evidences of intolerance for the substance.

*Nausea.* A few patients who received streptomycin, and who exhibited one or more of the aforementioned reactions, complained of nausea and, on occasions, they had vomited.

*Effects on Renal Function.* All patients who received streptomycin were carefully studied with regard to possible impairment of renal function. Determinations of blood urea have been made frequently on all patients who have received the substance. In no instance has there been any evidence of rising concentrations of blood urea. Likewise, in some instances, urea clearance tests have failed to reveal any significant change; in fact, as much as 150,000,000 units of fairly potent streptomycin has been administered, over a period of 42 days, to a single patient who had solitary kidney (average daily dose approximately 3,500,000 units) without evidence of interference with renal function.

On the other hand, repeated large doses of streptomycin at times have been followed by evidence of renal irritation. For example, in Case 7 (Table 1) the patient received 400,000 units of streptomycin intravenously every 3 hours for 3 doses. Albuminuria and microscopic hematuria developed; however, no evidence of permanent renal damage followed cessation of administration of the substance. This amount (3,200,000 units per day) is in excess of the average contemplated daily therapeutic dose.

*Effect on Liver Function.* As was suggested in an earlier paragraph, at the time this report was written, no conclusive evidence had been presented of interference with hepatic function following the use of streptomycin in amounts reported in this paper.

*Effect on the Hemolytotoxic System.* In all cases concerned in the present report, determinations of the hemoglobin content of the blood

were made frequently and erythrocyte, leukocyte and differential blood counts were made before, during and after administration of streptomycin. Likewise, blood smears were examined frequently for evidence of any morphologic change after short or prolonged treatment with streptomycin. In no instance has any effect been noted which could be attributed to the preparation.

**Summary.** The antibiotic substance, streptomycin, has been administered to a number of human beings in amounts which could, on a theoretic basis, be regarded as therapeutically effective. The number of patients concerned in the study is only partially represented by the 30 patients accounted for in the tables which accompany the paper. Approximately 10 others are referred to in the text. The material can be administered intravenously, intramuscularly or subcutaneously. The substance also can be administered by the intrathecal route, by nebulization or by the oral route. It would appear that if intermittent methods of parenteral administration are to be used, the substance should be administered at least every 3 or 4 hours in a manner similar to that which has been employed for administration of another antibiotic agent, penicillin.

It appears that diffusion of streptomycin into the cerebrospinal fluid does not readily take place unless large doses are administered. On the other hand, following parenteral administration, streptomycin is readily absorbed into the general circulation and is excreted for the most part in the urine. From the studies reported herein, it appears that diffusion of streptomycin through the placenta takes place and that streptomycin is available in the fetal circulation. Streptomycin also appears to be concentrated and excreted in the bile.

Serious and uncontrollable toxic reactions have not been encountered following administration of fairly large amounts of streptomycin in single or repeated injections. In some instances, streptomycin has been administered to patients for a considerable time without evidence of toxic reactions.

#### REFERENCES

1. FELDMAN, W. H., and HINSHAW, H. C.: Proc. Staff Meet., Mayo Clin., 19, 593, 1944.
2. HEILMAN, D. H.: Proc. Staff Meet., Mayo Clin., 20, 145, 1945.
3. HEILMAN, F. R.: Proc. Staff Meet., Mayo Clin., 19, 553, 1944.
4. HEILMAN, F. R.: Proc. Staff Meet., Mayo Clin., 20, 33, 1945.
5. JONES, D., METZGER, H. J., SCHATZ, A., and WAKSMAN, S. A.: Science, 100, 103, 1944.
6. ROBINSON, H. J., SMITH, D. G., and GRAESSLE, O. E.: Proc. Soc. Exp. Biol. and Med., 57, 226, 1944.
7. SCHATZ, A., and WAKSMAN, S. A.: Proc. Soc. Exp. Biol. and Med., 57, 244, 1944.
8. SCHATZ, A., BUGIE, E., and WAKSMAN, S. A.: Proc. Soc. Exp. Biol. and Med., 55, 66, 1944.
9. STEBBINS, R. B., and ROBINSON, H. J.: Proc. Soc. Exp. Biol. and Med., 59, 255, 1945.
10. WAKSMAN, S. A., and REILLY, H. C.: J. Infect. Dis., 75, 150, 1944.
11. WAKSMAN, S. A., BUGIE, E., and SCHATZ, A.: Proc. Staff Meet., Mayo Clin., 19, 537, 1944.

## THE ANTAGONISM OF LOCAL ANESTHETICS AGAINST THE SULFONAMIDES

BY BURNHAM S. WALKER, M.D., PH.D.

PROFESSOR OF BIOCHEMISTRY

AND

MATTHEW A. DEROW, M.D., PH.D.

INSTRUCTOR IN BACTERIOLOGY AND IMMUNOLOGY

BOSTON, MASSACHUSETTS.

With the Technical Assistance of ROSALYN ANN SWARTZ

(From the Departments of Biochemistry and Bacteriology, Boston Univ. School of Medicine, under a grant from the White Laboratories, Inc.)

THE inhibition of the antibacterial action of the sulfonamide drugs by procaine ("novocaine"), the most widely used of the local anesthetics, has been clearly demonstrated by Peterson and Finland,<sup>8</sup> who summarized the earlier literature in their report. Procaine, an ester of p-aminobenzoic acid, can be hydrolyzed, with liberation of free p-aminobenzoic acid, by esterases present in human tissues.<sup>5</sup> Thus the mechanism of inhibition of sulfonamides by procaine can be attributed to its structural similarity to a "natural" antagonist, p-aminobenzoic acid, and in all probability to the p-aminobenzoic acid actually formed by hydrolysis of procaine.

Keltch, Baker, Krahle and Clowes<sup>2</sup> found that 5 other esters of p-aminobenzoic acid which had local anesthetic properties were inhibitory to sulfonamide bacteriostasis. The same authors reported that another group of local anesthetics which were not esters of p-aminobenzoic acid or of substituted p-aminobenzoic acids, had no inhibitory effect. Winkler<sup>9</sup> similarly found inhibition by 3 esters of p-aminobenzoic acid, and no inhibition by a local anesthetic which was a quinoline derivative with no p-aminobenzoyl group.

At the request of Dr. C. W. Sondern, of the White Laboratories, Inc., certain substances with proved or putative local anesthetic action were studied by us with regard to their activity as sulfonamide-antagonists. Other substances, including many of those reported by the above-mentioned authors, were simultaneously investigated to serve as controls. The present report deals with these local anesthetics and other substances. We have repeated, in most cases confirmed, and in some cases extended the work of other investigators, and in addition presented data on a few substances not previously studied.

m-Aminobenzenesulfonamide has no activity against microorganisms comparable to that of sulfanilamide. This is in accordance with a hypothesis proposed by Kumler and Halverstadt<sup>3</sup> based upon the possible existence of resonance isomers of sulfanilamide which are impossible with the meta configuration. On purely theoretical grounds it would not be expected that either o-aminobenzoic acid or m-aminobenzoic acid would act in a manner comparable with p-aminobenzoic acid in regard to inhibition of the sulfonamides. Landy and Wyen<sup>4</sup> reported no antisulfanilamide action demonstrable with either the



ortho or the meta isomer. Benigno,<sup>1</sup> however, is reported in an abstract of a paper published in 1943 to have stated that the actions of o- and m-aminobenzoic acids are similar to that of p-aminobenzoic acid but much weaker. Therefore, these substances, and certain local anesthetics derived from one of them, were consequently included in our study.

**Methods of Investigation.** Our procedure was based upon the method used by Peterson and Finland.<sup>8</sup> Sulfathiazole (0.2 ml. of 0.002 molar solution) was mixed with equine blood (0.5 ml.) and a suspension (0.1 ml.) of a known number of organisms (hemolytic streptococcus, N.Y.5 strain, or in a few experiments pneumococcus Type III). To this was added the local anesthetic or other drug under investigation in known molar concentration and in a volume of 0.1 ml. Under these conditions the molar ratio<sup>7</sup> of sulfathiazole to "inhibitor" could easily be calculated.

The only unmeasured variable in this system was the amount of inhibiting substances in the blood. To control this doubtful factor, each experimental run was accompanied by control runs, using an equal number of tubes containing blood and organisms alone, and an equal number containing blood, organisms, and sulfathiazole. Volumes were kept consistently at 0.9 ml. total by the addition of sterile saline solution. Blood was used in all experiments, again following the example of Peterson and Finland,<sup>8</sup> since its presence provides a closer approximation to conditions *in vivo*, and since it serves as a quick indicator of bacterial growth. Incubation was carried on for 48-hour periods at 37° C., with mechanical rocking replacing the rotating drum of Peterson and Finland. Because of mechanical difficulties, all experiments were not rocked for the full time. No changes in results could be attributed to this change in technique. All negative or doubtful tubes were subcultured. Organisms were grown and diluted in tryptic digest broth.

A typical experiment is shown in Table I. The significant observations to

TABLE I.—RESULTS OF A TYPICAL EXPERIMENT SHOWING MINIMAL INOCULUM SURVIVING WITH SULFATHIAZOLE ALONE AND WITH AN INHIBITING AND NON-INHIBITING LOCAL ANESTHETIC

	Logarithm of total initial number of organisms (hemolytic streptococci, N.Y.5 strain)					
	6	5	4	3	2	1
Control . . . . .	+	+	+	+	0	0
Sulfathiazole, $4.4 \times 10^{-4}$ M. . . . .	+	+	0	0	0	0
Sulfathiazole plus procaine-HCl, $1.1 \times 10^{-3}$ M.* . . . .	+	+	+	+	+	0
Sulfathiazole plus procaine-HCl, $1.1 \times 10^{-4}$ M.† . . . .	+	+	+	+	0	0
Sulfathiazole plus benzyl alcohol, $1.1 \times 10^{-3}$ M.* . . .	+	+	0	0	0	0
Sulfathiazole plus benzyl alcohol, $1.1 \times 10^{-4}$ M.† . .	+	+	0	0	0	0

+ = growth in 48-hour subculture. 0 = 48-hour subculture sterile.

\* Molar ratio, 0.4.

† Molar ratio, 4.

be made are: (1) the logarithm of the number of organisms in the smallest inoculum (log MVI) surviving in the control tubes, which contain blood and broth alone; (2) the logarithm of the minimal viable inoculum in the tubes containing sulfathiazole in addition to blood and broth; and (3) the logarithm of the minimal viable inoculum in experimental tubes containing blood and broth, sulfathiazole and the substance under test for inhibiting effect. The difference (2) minus (3) gives us the logarithm of the ratio MVI for sulfathiazole/MVI for sulfathiazole plus inhibitor. The magnitude of this difference is a rough measure of inhibitory action and may be considered an "index of inhibition." If this is positive, it indicates inhibition; if it is zero, it indicates no effect; if it is negative, it indicates additional bacteriostatic or bactericidal effect.

**Results.** In several experiments the inhibitory action of procaine was compared with that of p-aminobenzoic acid. If concentrations are figured in terms of molarity, there is no quantitative difference between the inhibitory effect of the free acid and of the ester. A typical experiment is shown in Table 2.

TABLE 2.—RESULTS OF A TYPICAL EXPERIMENT SHOWING AGREEMENT IN INHIBITORY EFFECT BETWEEN EQUI-MOLAR CONCENTRATIONS OF PROCAINE AND OF P-AMINOBENZOIC ACID

	Logarithm of total initial number of organisms (pneumococci Type III)					
	6.1	5.1	4.1	3.1	2.1	1.1
Control . . . . .	+	+	+	+	+	0
Sulfathiazole, $4.4 \times 10^{-4}$ M. . . . .	+	+	+	0	0	0
Sulfathiazole plus p-aminobenzoic acid, $1.1 \times 10^{-3}$ M.*	+	+	+	+	+	0
Sulfathiazole plus procaine-HCl, $1.1 \times 10^{-5}$ M.*	+	+	+	+	+	0

\* Molar ratio, 40.

The experiment in Table 2 and a few preliminary experiments were done with Type III pneumococcus as the test organism, following the example of Peterson and Finland.<sup>8</sup> For the main experimental series Group A hemolytic streptococcus became the organism of choice, since it offered fewer cultural difficulties. All experiments with hemolytic streptococci are summarized in Table 3.

TABLE 3.—INDICES OF INHIBITION OF ALL SUBSTANCES TESTED AGAINST SULFATHIAZOLE USING HEMOLYTIC STREPTOCOCCUS, N.Y.5 STRAIN, AS TEST ORGANISM

Substance	Molar ratio (sulfathiazole/inhibitor)			
	400	40	4	0.4
p-aminobenzoic acid* . . . . .	1	2		
Procaine* . . . . .	..	2	2	3
o-aminobenzoic acid* . . . . .	..	..	0	0
m-aminobenzoic acid* . . . . .	..	..	0	0
Orthoform . . . . .	..	..	0	0
3-amino-4-hydroxypropylbenzoate . . . . .	..	0	0	0
3-amino-4-hydroxybenzoic acid . . . . .	..	..	0	0
Allypin* . . . . .	..	0	0	0
Apothesine* . . . . .	..	0	0	0
Benzyl alcohol . . . . .	..	0	0	0
Cocaine* . . . . .	..	0	0	0
Diothane* . . . . .	..	0	0	-1
Metycaine* . . . . .	..	0	0	0
Nupercaine* . . . . .	..	-1	-1	-1
Phenacaine* . . . . .	..	-1	-1	-1
Tetracaine* . . . . .	..	0	0	0

\* The starred substances have been previously studied and reported by other investigators. They are included here in agreement with the previous reports.<sup>2,4,5</sup>

The results outlined in Table 3 confirm the results of previous investigators in the following respects: (1) p-aminobenzoic acid and its ester procaine show definite evidence of inhibition; (2) local anesthetics which are not esters of p-aminobenzoic acid show no such inhibition; (3) tetracaine, an ester of p-butylaminobenzoic, shows no inhibition.

Benigno,<sup>1</sup> in an article which we have seen only in abstract, claims a weak antisulfonamide action for o- and m-aminobenzoic acid. This is not confirmed by our work. Three derivatives of m-aminobenzoic

acid (orthoform N.N.R., which is 3-amino-4-hydroxymethylbenzoate, also 3-amino-4-hydroxypropylbenzoate, and 3-amino-4-hydroxybenzoic acid) were also found to be without inhibitory action against sulfathiazole.

Certain of the local anesthetics studied show not only no inhibitory effect against the sulfonamide, but an actual additional antibacterial effect. This was true of nupercaine and phenacaine, and to a less degree of diothane.

**Summary.** 1. The inhibitory effect of procaine has been found exactly comparable, mol for mol, with that of p-aminobenzoic acid upon sulfathiazole.

2. O-aminobenzoic acid and m-aminobenzoic acid are without inhibitory effect upon sulfathiazole.

3. Three derivatives of m-aminobenzoic acid (3-amino-4-hydroxymethylbenzoate (orthoform, N.N.R.), 3-amino-4-hydroxypropylbenzoate, and 3-amino-4-hydroxybenzoic acid) are likewise without inhibitory effect.

4. The work of previous investigators demonstrating no antisulfonamide action of local anesthetics other than the derivatives of p-aminobenzoic acid is confirmed.

#### REFERENCES

1. BENIGNO, P.: Arch. f. exp. Path. u. Pharm., 199, 265, 1943; Chem. Abstr., 37, 5489, 1943.
2. KELTCH, A. K., BAKER, L. A., KRAHL, M. E., and CLOWES, G. H. A.: Proc. Soc. Exp. Biol. and Med., 47, 533, 1941.
3. KUMLER, W. D., and HALVERSTADT, I. F.: J. Am. Chem. Soc., 63, 2182, 1941.
4. LANDY, M., and WYENO, J.: Proc. Soc. Exp. Biol. and Med., 46, 59, 1941.
5. LAWRENCE, C. A., and GOETCHIUS, G. R.: Proc. Soc. Exp. Biol. and Med., 57, 180, 1944.
6. LEGGE, J. W., and DURIE, E. B.: Med. J. Australia, 2, 561, 1942.
7. McILWAIN, H.: Brit. J. Exp. Path., 23, 265, 1942.
8. PETERSON, O. L., and FINLAND, M.: Am. J. Med. Sci., 207, 166, 1944.
9. WINKLER, A.: Zentralbl. f. Bakteriol., 1 Abt., Orig., 151, 106, 1944.

### THE PENETRATION OF PENICILLIN INTO JOINT FLUID FOLLOWING INTRAMUSCULAR ADMINISTRATION

BY CAPT. VICTOR G. BALBONI, M.C., A.U.S.

1ST LIEUT. IRVING M. SHAPIRO, Sn.C., A.U.S.

AND

MAJOR DAVID M. KYDD, M.C., A.U.S.

ASHBURN GENERAL HOSPITAL, MC KINNEY, TEXAS

PENICILLIN administered to man by the intramuscular, intravenous or subcutaneous routes has been shown to appear rapidly in the blood serum, to appear in the bile in higher concentrations than in the serum and to be excreted in the urine.<sup>1,11,12</sup> It is not found in detectable amounts in the saliva, nor in the normal spinal fluid,<sup>11</sup> but is present in the spinal fluid when the meninges are inflamed.<sup>5</sup> Penicillin has been detected in low concentration in the red cells,<sup>11</sup> lachrymal secretions,<sup>11</sup> and even to a minimal extent throughout the tissues of the

eyeball excepting the ocular lens.<sup>15,16</sup> Earlier studies<sup>1,11</sup> have not clarified the extent to which penicillin is transferred to the synovial fluid. This has resulted in some doubt as to whether following systemic administration a sufficient amount of penicillin would reach the joint fluid to be effective in the treatment of the purulent arthritides. However, clinical observations by both Herrell<sup>8,9</sup> and by Dawson<sup>6</sup> indicate that effective antibacterial amounts of penicillin may be obtained in joint fluid by systemic administration despite the equivocal observations of Linner,<sup>10</sup> Robinson,<sup>14</sup> and Anderson.<sup>2</sup>

The findings of Herrell<sup>8,9</sup> and of Dawson<sup>6</sup> are of considerable importance for though the local instillation of penicillin into a joint lends itself readily to the treatment of a purulent arthritis of one of the larger joints, it is less applicable where one or more small joints are affected. The present study was undertaken to define more clearly the extent to which penicillin administered intramuscularly penetrates into joint fluid.

Seven patients with hydrarthrosis affecting one or more joints were studied: 5 of the patients had typical rheumatoid arthritis and 2 an atypical disease which was probably rheumatoid arthritis. In Case 4 alone was the joint studied severely inflamed. Cases 1, 2, 5 and 6 received 25,000 units of penicillin in 2.5 ml. of normal saline intramuscularly every 3 hours. Cases 3, 4 and 7 received 40,000 units.

In each instance samples of serum and joint fluid were obtained simultaneously  $\frac{1}{2}$ , 1, 2 and 3 hours after the subject had received the 8th dose of penicillin. In 4 instances, Cases 2, 3, 5 and 6, samples were obtained 3 hours after the 16th dose and in Case 3 additional material was obtained 3 hours after the 24th dose.

**Methods.** The concentrations of penicillin in both the blood sera and the joint fluids were determined by the cup assay method as modified by Cholden.<sup>3</sup> The diameter of each cup was 9 mm. *Staphylococcus aureus* which was sensitive to 0.016 units of penicillin per ml. was used as the test organism. It was grown in nutrient broth for 18 hours and then 0.1 ml. was inoculated into 20 ml. of melted nutrient agar and plates were poured. The undiluted synovial fluids and blood sera were delivered in 0.1 ml. amounts into the cups, and after incubation at 37° C. for 18 to 24 hours the areas of inhibition of growth were measured. As suggested by Foster and Woodruff<sup>7</sup> a standard penicillin curve was determined with each day's experiment, and the amount of penicillin present in the sera and joint fluids interpolated from this curve.

**Results** (See Table 1). In all cases penicillin was found to penetrate readily into the joint fluids resulting in essentially equal amounts of penicillin in the joint fluid and blood serum 1 hour after its administration. As previous investigators have shown<sup>11</sup> the serum concentrations fell rapidly after 1 hour and at the end of 3 hours little or no penicillin was detectable in the serum. However, our results show that in the joint fluids the concentration of penicillin decreases more slowly, and that there are appreciable amounts of penicillin present in the joint fluid 3 hours after its administration. This slow loss of penicillin from joint fluid is in agreement with the work of Rammekamp and Keefer<sup>11</sup> who detected penicillin in joint fluid 13 hours after penicillin was injected directly into the joint. Though penicillin disappears

from the joint fluid more slowly than from blood serum, it does not accumulate. This is shown in Table 1 by the concentrations found in the joint fluid after the 2nd day of penicillin administration and in 1 instance after the 3rd day.

TABLE 1.—PENICILLIN IN BLOOD SERUM AND JOINT FLUID

Case No.	Wt. (lb.)	Dose I.M. (units)	Joint	W.B.C. joint (fluid)	Penicillin (units/ml.)	1st day				2nd day 3 hr.	3rd day 3 hr.
						½ hr.	1 hr.	2 hr.	3 hr.		
1	150	25,000	Knee	10,000	Blood serum	0.24	0.20	0.05	0.0		
					Joint fluid	0.24	0.15	0.10	0.05		
2	155	25,000	Knee	2,500	Blood serum	0.20	0.10	0.0	0.0	0.07	
					Joint fluid	0.20	0.20	0.05	0.0		
3	170	40,000	Knee	5,000	Blood serum	0.27	0.20	0.12	0.05	0.14	0.14
					Joint fluid	0.24	0.24	0.20	0.14		
4	177	40,000	Ankle	6,500	Blood serum	..	0.40	0.10	0.0		
					Joint fluid	..	0.30	0.15	0.05		
5	134	25,000	Knee	2,300	Blood serum	0.30	0.27	0.17	0.05	0.15	
					Joint fluid	0.20	0.22	0.22	0.17		
6	110	25,000	Knee	10,000	Blood serum	0.30	0.20	0.12	0.05	0.15	
					Joint fluid	0.17	0.20	0.20	0.15		
7	214	40,000	Knee	5,000	Blood serum	0.22	0.19	0.12	0.05		
					Joint fluid	0.17	0.19	0.15	0.13		

Rammelkamp and Keefer<sup>13</sup> have shown that a marked antibacterial effect against *Staphylococcus aureus* is obtained in whole blood and serum with concentrations of 0.039 and 0.156 Florcy units of penicillin per ml. Hemolytic streptococci, pneumococci, meningococci and gonococci are generally considered more sensitive to penicillin than *S. aureus*.<sup>4,6,8</sup> The joint fluid of the cases studied 1 hour after administration of penicillin showed amounts of penicillin varying from 0.15 to 0.24 units per ml., levels well within the antibacterial level for staphylococci. The 3 hour determinations of 6 of the 7 joint fluids contained 0.05 to 0.17 units per ml., amounts still in the lower range of antibacterial activity for staphylococci. Thus our findings indicate that amounts of penicillin which are antibacterial for the common pathogens invading joints are obtained in the synovial fluid by the intramuscular administration of penicillin in the doses discussed.

**Summary.** 1. Penicillin was administered intramuscularly to 7 cases of hydrarthrosis. Concomitant blood serum and joint fluid penicillin assays were determined at ½, 1, 2 and 3 hour intervals.

2. Penicillin when administered intramuscularly in 25,000 and 40,000 unit doses at 3 hour intervals was found to penetrate rapidly into joint fluid and attain levels comparable with those attained in blood serum.

3. Maximum antibacterial quantities of penicillin were found to persist longer in the joint fluid than in the blood serum.

4. Penicillin did not tend to accumulate in joint fluid.

#### REFERENCES

1. ABRAHAM, E. P., CHAIN, E., FLETCHER, C. M., GARDNER, A. D., HEATLEY, N. G., JENNINGS, M. A., and FLOREY, H. W.: Further Observations on Penicillin, *Lancet*, 2, 177, 1941.
2. ANDERSON, D. G.: Penicillin, *Bull. New England Med. Center*, 6, 145, 1944.
3. CHOLDEN, L. S.: A Simplified Technique for Agar Cup Assay of Penicillin, *J. Bact.*, 47, 402, 1944.

4. COMROE, B. I.: *Arthritis and Allied Conditions*, Philadelphia, Lea & Febiger, p. 1250, 1944.
5. COOKE, J. V., and GOLDRING, D.: The Concentration of Penicillin in Various Body Fluids During Penicillin Therapy, *J. Am. Med. Assn.*, 127, 80, 1945.
6. DAWSON, H. M., and HOBBY, G. L.: The Clinical Use of Penicillin; Observations in 100 Cases, *J. Am. Med. Assn.*, 124, 611, 1944.
7. FOSTER, J. W., and WOODRUFF, H. B.: Microbiological Aspects of Penicillin: VI. Procedure for the Cup Assay for Penicillin, *J. Bact.*, 47, 43, 1944.
8. HERRELL, W. E., NICHOLS, D. R., and HEILMAN, D. H.: Penicillin: Its Usefulness, Limitations, Diffusion and Detection With Analysis of 150 Cases in Which It Was Employed, *J. Am. Med. Assn.*, 125, 1003, 1944.
9. HERRELL, W. E.: *Penicillin and Other Antibiotic Agents*, Philadelphia, Saunders, p. 77, 1945.
10. LINNER, J. H.: Suppurative Myositis and Purulent Arthritis Complicating Acute Gonorrhea; Report of a Case, *J. Am. Med. Assn.*, 123, 757, 1943.
11. RAMMELKAMP, C. H., and KEEFER, C. S.: The Absorption, Excretion and Distribution of Penicillin, *J. Clin. Invest.*, 22, 425, 1943.
12. RAMMELKAMP, C. H., and HELM, J. D., JR.: Excretion of Penicillin in Bile, *Proc. Soc. Exp. Biol. and Med.*, 54, 31, 1943.
13. RAMMELKAMP, C. H., and KEEFER, C. S.: Penicillin: Its Antibacterial Effect in Whole Blood and Serum for the Hemolytic Streptococcus and Staphylococcus Aureus, *J. Clin. Invest.*, 22, 649, 1943.
14. ROBINSON, J. N.: Discussions on Penicillin, *Brit. Med. J.*, 2, 655, 1943.
15. STRUBLE, G. C., and BELLOW, J. G.: Studies on the Distribution of Penicillin in the Eye and Its Clinical Application, *J. Am. Med. Assn.*, 125, 685, 1944.
16. VON SOLLMAN, L., and MEYER, K.: Penetration of Penicillin Into the Eye, *Arch. Ophth.*, 31, 1, 1944.

## TYPHOID BACILLURIA AND UROLITHIASIS

BY F. DREYFUSS, M.D.

ASSISTANT IN MEDICINE

AND

J. ROTH, M.D.

ASSISTANT IN PEDIATRICS

JERUSALEM, PALESTINE

(From the Department of Medicine A and the Department of Pediatrics B of the Hadassah-Rothschild-University-Hospital)

THE conditions under which an individual becomes a carrier of typhoid bacilli present considerable interest from a clinical as well as from an epidemiologic point of view. Excretion of typhoid bacilli in the stools is usually caused by specific infection of the bile passages where the bacillus thrives as in a culture medium. This process is particularly apt to occur in patients whose bile passages are in a state of functional or anatomic impairment following previous disease.

Transient bacilluria is a common event in typhoid fever and, when carefully looked for, is detected in between 20 to 50% of cases (Schottmueller,<sup>6</sup> Young<sup>7</sup>). Persistent urine carriers, however, are said to be considerably rarer than stool carriers, their percentage amounting to a few tenths of 1% up to 3% of convalescents, according to different statistics. In the case of these urinary carriers the determining factors of persistent bacilluria are a matter of conjecture.

It is not within the scope of this communication to review the urologic complications described in typhoid fever. Observations about pathologic conditions of the urinary tract connected with typhoid bacilluria are particularly scarce. Young,<sup>7</sup> Harries<sup>1</sup> and asso-

ciates mention occasional suppuration of the kidneys due to *B. typhosus*. Even cystopyelitis is usually regarded as an uncommon complication. We were able to find only one reference to the simultaneous occurrence of nephrolithiasis and typhoid bacilluria: C. Hirsch<sup>3</sup> quotes Krause, who saw among 24,500 typhoid convalescents during several years 0.2 to 3.3% urine carriers and simply mentions 5 cases of nephrolithiasis among them.

According to the experience of urologic practice dealing with urinary infections and urolithiasis the finding of typhoid bacilli in the urine together with a stone seems to be very rare. The statistics of H. L. Harrington,<sup>2</sup> for instance, do not mention a single case of typhoid infection among 480 cases of urolithiasis.

Within 1½ years, 4 cases of urolithiasis together with typhoid bacilluria have been observed in the Medical Dept. A. and the Pediatric Dept. B. of our hospital. Their case histories are presented with the view of contributing material to the solution of the carrier problem.

The procedure for isolation of typhoid bacilli from the urine and their identification as performed in the Bacteriological Laboratory of our hospital (Chief, Dr. Gurewitz) is as follows: The urine is centrifuged and a loopful of the sediment streaked out on a McConkey plate. To the remaining sediment 5 cc. of ox bile and nutrient broth in equal parts are added. In positive cases a pure culture (grayish, transparent colonies) of gram-negative bacilli is obtained after 24 hours. A few colonies of this growth are transferred separately into tubes containing double-sugar (Russell's) medium. On this medium typhoid bacilli show the following behavior: no gas is formed but slight acidity in the butt of the tube is produced. The sugar row used afterwards for identification is as follows: acid and no gas from dextrose, maltose and mannitol, no acid on lactose; indol not formed. Then an agglutination test is carried out using an anti-serum of a titer of 1:2000.

Blood is taken for culture into bile broth and after incubation of 24 hours a loopful is streaked out on a McConkey plate and the procedure described above is followed.

According to this procedure the typhoid nature of the bacilli in all of our cases was established.

**Case Histories.** CASE 1. A. J., 19 years old, was admitted to the Surgical Dept. B of this hospital in December 1941. He had a stone in the right ureter and another one in the left kidney. He suffered from pain and showed hematuria. His blood pressure was 150/85. A ureterotomy was performed and the stone removed (Dr. Kook). Urine culture revealed *Staphylococcus aureus* and *B. proteus* before and after operation. The stone contained urates, phosphates and oxalates. His recovery was delayed briefly by mild and short postoperative bronchopneumonia. In February 1942, he returned to us because of pain in the left lumbar region. He emphasized even on close questioning that he had felt well all the time except for the pain he mentioned, and that he had had no fever since leaving the hospital. Urine analysis showed 1 to 2 erythrocytes and 80 to 100 leukocytes per high power field. *B. typhosus* was cultured from the urine. A second operation was performed and a stone was removed from the left kidney (Dr. Kook). Typhoid bacilli were cultured from within this stone. The temperature rose to 40° one day after operation;

high fever lasted for 11 days accompanied by relative bradycardia until the temperature finally dropped by lysis. His consciousness was slightly impaired, his tongue was heavily coated. He had the appearance of a patient sick with typhoid. The Widal reaction was positive 1 day after operation, but the organism was not cultured from the blood or stool, whereas urine cultures were always positive during his stay in the hospital. Pyuria persisted, *B. proteus* and *B. pyocyaneus* also being found in the urine. A dose of 24.5 gm. of sulfapyridine was of no avail. He remained under observation of the medical clinic and although he felt well all the time, urine cultures remained positive. Mandelic acid was administered following the suggestion of Kleeberg<sup>4,5</sup> who successfully used this material in a number of typhoid cases; two courses failed, however, to rid him from the infection. In June 1943, pain in the left lumbar region reappeared and reached the intensity of colics accompanied by fever. On admission to the Medical Dept., the Widal agglutination test showed a titer of 1:1000 for *B. typhosus* and 1:200 for *B. gaertner*. The urine contained many red and a few white cells and although a Roentgen picture failed to reveal a stone, its presence was clinically almost certain. The urine showed again a heavy growth of *B. typhosus*, this finding being positive also in specimens taken separately from both ureters. After cystoscopy his temperature rose to 40° for 4 days accompanied again by bradycardia and leukopenia. He received 25 gm. of sulfapyridine, which finally cleared the infection, a result which since then has been verified several times.

CASE 2. A. Ch., 36 years old, was admitted to the Medical Dept. A, in June 1942, on the 11th day of his disease. He was ill with typhoid fever of a fairly severe form but not very toxic in character. Blood cultures were positive several times. Fever did not drop for several months. Because of this unusually prolonged fever a thorough clinical, laboratory and Roentgen ray examinations were performed. Besides a mild and short bronchopneumonia no focus of infection was revealed. It must be stressed that the findings of urine examinations and cultures were negative. On August 21, for the first time, many leukocytes and a few erythrocytes were found in the urine and this finding persisted for about 1 month after which period examinations became negative. On October 18, an intravenous pyelography was performed and a small stone in the middle third of the left ureter as well as dilatation of the urinary passages above the stone were detected. On October 19, *B. typhosus* was cultured from a urine specimen for the first time, on the 26th the patient had a typical left side renal colic. The patient who had been carefully questioned several times only then recalled that about 1 year earlier he had had a similar attack. He was not able to remember on which side—but remembered to have been advised by his physician to have a Roentgen ray taken, a stone being suspected. He had disregarded this advice and neglected the matter. Simultaneously with the attack mentioned above, his temperature now rose to 40°. On October 25, the stone was removed from the left ureter (Dr. Ehrlick). The urine remained infected by typhoid bacilli for more than at least 1 month, until he finally left the hospital. Both mandelic acid and sulfapyridine administered in several series failed to influence the typhoid fever and mandelic acid did not succeed to clear his urine after the operation. To sum up, in this case of typhoid a stone in the ureter apparently existed before specific bacilluria started.

CASE 3. L. K. K., a boy, 8 years old, was admitted to Pediatric Dept. B on April 21, 1941, in a severe general condition, following a febrile disease of 10 days duration. The diagnosis was typhoid fever complicated by otitis media. The urine was normal. No particular treatment was administered and on the 30th day of his disease the temperature dropped to normal. Ten days later, the boy was sent home, no cultures of the urine having been made.

About  $\frac{1}{2}$  year later the patient was brought to the out-patient clinic, showing signs of balanitis and paraphimosis. The reason for this balanitis was seen in a paraurethritis and for further investigation the boy was transferred to the skin clinic. Since the local condition was not improved and no reason for its



persistence could be detected, the patient was again admitted to the Pediatric Service. This time many leukocytes were found in the urine, in the first as well as in the second portion, and *B. typhosus* was cultured from the urine. In pus from the paraurethra, streptococci were found. An attempt to influence the balanitis by sulfonamide medication was unsuccessful. When searching for the reason of pyuria and typhoid bacilluria, Roentgen ray examination revealed an "ausguss" stone in the left kidney pelvis and dilated calices. During his stay in the hospital subfebrile temperatures were frequent and urine cultures always showed growth of *B. typhosus*. A severe pyoderma and eczema of the head and face made surgical intervention inadvisable at least for a certain time, and only after his skin infection had cleared up, a nephrolithotomy was performed (Dr. E. Joseph). The patient ran a febrile course for the first 10 postoperative days. During the early postoperative period typhoid bacilli disappeared from the urine but after a few days urine cultures became positive again. Mandelic acid, in a 6 gm. daily dose given for 12 days, did not clear the infection. The boy finally left the hospital in a good condition, but still showing pyuria excreting typhoid bacilli.

In this case *B. typhosus* was found 6 months after the final stage of typhoid fever. The urologic examination performed because of pyuria and bacilluria revealed nephrolithiasis.

CASE 4. Y. N., a boy, 11½ years of age, was admitted to the Pediatric Dept. B. on Dec. 18, 1942, because of high fever which was diagnosed as typhoid. The urine was normal. He received treatment by autohemoinjections following a method introduced by Dr. E. Rabinovitz. On the 13th day of the disease his temperature dropped to normal. Ten days later the temperature rose again, this time showing an irregular course of a character not usually observed in recurrences of typhoid. His temperature finally became subfebrile. The only abnormal findings in this period were pyuria and urine cultures positive for *B. typhosus*. Stool cultures were negative. On Roentgen ray examination of the urinary tract a large "ausguss" stone was found in the right kidney pelvis and a smaller one in the right ureter. During cystoscopy urine specimens were separately taken from both ureters for bacteriologic examination. Only the specimen taken from the right, i. e., stone carrying side, showed *B. typhosus*. The boy's blood pressure was 125/80 at that time, a blood pressure definitely too high for this age. It was decided to remove the stone from the ureter first and this operation was performed (Dr. E. Joseph). When recovering from this operation, the boy fell ill with a severe and stubborn pyoderma. His blood pressure, incidentally, rose to 135/90. When the boy recovered at last from the skin complication the removal of the stone from the kidney was decided upon. But, on opening the lumbar region a big paranephritic abscess was cut open and the operative procedure was brought to an end by draining this abscess; when the wound cavity finally closed, the child had to be sent for convalescence because of his bad general condition. In this case urolithiasis and typhoid bacilluria persisted a few days after the fever had dropped. To our regret and in spite of our efforts we did not succeed in getting in touch with these 2 boys for follow-up examination.

A definite relation between bacilluria in general and pathologic conditions of the urinary tract exists. Heavy and prolonged excretion of bacilli in the urine may produce at least two urologic disease conditions—acute or chronic inflammation and development of stones. the resulting cystopyelitis is in itself a contributory factor for the formation of stones. On the other hand, stones similar to other disturbances of the urinary flow tend to maintain infections otherwise probably transient in character.

In the 2 adult cases lithiasis most probably existed before the

typhoid infection. It seems evident that a causal relationship exists between prolonged bacilluria and lithiasis. The particular conditions which are produced by stones in the urinary tract (urostasis, cystopyelitis) tend to prolong a temporary excretion of bacilli, in itself so frequent in typhoid, to a continuous bacilluria, a mechanism which is generally recognized as operative in urinary infections. As for the 2 children the circumstances are less clear. With both of them, lithiasis was diagnosed after their having recovered from typhoid. In both cases the stones showed the typical shape of an "ausguss" stone, as commonly found complicating urinary infections. It is also known that such a stone sometimes needs only a short time for its formation. We have seen cases, in septicemia, where a stone of this type developed within 2 weeks. Moreover, when we take into consideration the comparative rarity of urinary calculi in children it seems probable that those stones were formed in consequence of an acute infection by typhoid bacilli. We are, of course, not able to deny definitely their existence prior to the typhoid fever since urologic and anamnestic data are lacking for the period anteceding typhoid.

We believe that urinary calculi may condition a prolonged typhoid bacilluria, or, if formed as the result of the bacilluria, may maintain it persistently. We consequently think it advisable to perform a Roentgen ray examination of the urinary tract in urinary excretion of typhoid bacilli.

**Summary.** It is pointed out that, whereas the conditions under which a patient becomes a permanent excretor of typhoid bacilli from the bowels are known to a certain extent, information about urologic lesions conditioning typhoid bacilluria is limited.

Four cases are reported in which typhoid bacilluria coincided with urolithiasis: in 2 adult cases urolithiasis existed before the excretion of typhoid bacilli; in 2 children, stone formation seemed to follow typhoid bacilluria.

In the light of experience with other infections of the urinary tract the relationship between typhoid bacilluria and urolithiasis is discussed and its possible clinical and epidemiologic importance is emphasized.

**Conclusion.** From the foregoing it is evident that the relationship between urolithiasis and typhoid bacilluria is of clinical and epidemiologic importance.

#### REFERENCES

1. HARRIES, E. H. R., MITMAN, M., and DALEY, W. A.: *Clinical Practice in Infectious Diseases*, Edinburgh, 1940.
2. HARRINGTON, H. L.: *J. Urol.*, 44, 507, 1940.
3. HIRSCH, C.: *In Pathologie und Therapie inneren Krankheiten*, 2, Part 3, Berlin and Wien, Urban und Schwarzenberg, p. 324, 1923.
4. KLEEGER, J.: *Trans. Roy. Soc. Trop. Med. Hyg.*, 35, 191, 1941.
5. KLEEGER, J.: *Acta med. Orient.*, 2, 187, 1943.
6. SCHOTTMUELLER, H.: *In Handbueh der inneren Medizin*, 1, Part 2, Berlin, Springer, p. 1009, 1925.
7. YOUNG, H. H., and DAVIS, D. M.: *Young's Practice of Urology*, 1, Philadelphia and London, Saunders, p. 96, 1926.

## HUMAN INFECTION WITH BACTERIUM NECROPHORUM

BY CAPT. I. J. GREENBLATT, SN.C., A.U.S.\*

AND

A. P. GREENBLATT

PITTSBURG, CALIFORNIA.

(From the Army Service Forces, Camp Stoneman)

THE last decade has seen the general use of anaerobic techniques in clinical bacteriology. This has contributed to the isolation and recognition of organisms which do not grow under the ordinary aerobic bacteriologic techniques formerly held to be adequate for clinical purposes. Media containing the sulfhydryl compounds (thioglycolic acid or its salts, cysteine and so forth) are used today to obtain anaerobic conditions. It has been our policy for some years to inoculate all material sent to the laboratory for bacteriologic studies into media containing thioglycolic acid, as well as the usual standard aerobic media. As a result, we were able to isolate and identify *B. necrophorum* from 3 human cases, an organism which usually is found only in domesticated animals.

Buhler, Seely and Dixon<sup>1</sup> have reviewed the literature of *B. necrophorum* in man. One case presented by Cunningham<sup>2</sup> had pulmonary involvement, but the organism was identified after postmortem examination. Shaw and Bigger<sup>3</sup> reported the isolation of *B. necrophorum* from the sputum of a male Negro with a lung abscess, who made an uneventful recovery after surgical intervention.

Dack and his co-workers<sup>3</sup> have reported the largest series of cases of infection with *B. necrophorum* in man. Their criteria of identification was similar to that of Orcutt<sup>4</sup> who studied the organisms obtained from infected domesticated animals.

**Case Reports.** CASE 1. M. J. L., white, 37 year old male, admitted with history of chills, fever, and a productive cough present for 6 days prior to admission. Past history was entirely negative and there was no contact with animals. He complained of a sharp pain on the right chest wall extending back to the right scapula. Physical examination showed a well-developed, alert subject with a foul breath. Moist crackling râles were heard at the right base. The temperature was 38.8° C. Roentgen ray findings suggested a possible lung abscess. Laboratory examinations were negative except for a leukocytosis (16,400 per c.mm., 84% neutrophils) and a foul smelling sputum having a butyric acid-like odor. The aerobic culture revealed little of significance. Anaerobically, a pleomorphic, long-branched and occasionally filamentous organism was isolated. It failed to grow aerobically and on 2 occasions the organism was lost on transplants. It fermented glucose, maltose and levulose. Gelatin was not liquefied. Indole was obtained from tryptophane broth. A green zone appeared at the end of 10 hours around each colony when exposed to air after anaerobic incubation for 3 days on blood agar plates. The organism failed to reduce nitrates and did not produce H<sub>2</sub>S. A number of transplants were required to obtain the organism in pure culture because

\* Present address 1280 East 18th Street, Brooklyn 30, N. Y.

of an accompanying gamma streptococcus. Regimen of sulfadiazine was instituted. Twenty-four gm. over a 4 day period was without effect on sputum production or odor. The patient was quite uncomfortable and complained of "chest" pains. Iodides and arsenicals over a period of next 11 days were ineffective. The patient's temperature remained "spikey." The Roentgen ray examination after the 13th hospital day showed no improvement. Daily sputum amounted to approximately 400 cc. A thoracotomy was performed on the 19th day after admission and the patient began to improve rapidly. He was discharged on the 11th week after surgery. The sera agglutination as well as complement fixation were positive for *B. necrophorum* 7 weeks after discharge from the hospital. A suspension of the organisms in 1 cc. saline introduced subcutaneously into 2 rabbits produced the typical necrotic lesions characteristic of *B. necrophorum* infection.

CASE 2. A 22 year old white girl with arrested pulmonary tuberculosis complained of a gradually increasing tenderness in the right axilla for 4 days. No history of exposure to animals was given. She was afebrile on admission but developed an elevated temperature (38° C.) on the 2nd hospital day. A fluctuating, tender, walnut-sized mass was felt on palpation. After 3 days on sulfadiazine and hot magnesium sulfate soaks, the abscess was incised. About 20 cc. of ill-smelling pus welled out. The abscess was evacuated, flushed with 5% sodium sulfadiazine. The wound drained for 6 days and then slowly closed without further ado. She was discharged on the 17th day after hospitalization.

Direct smear from the pus showed a small gram-negative, branched organism. It was a strict anaerobe and proved to be *B. necrophorum*. The complement fixation test was positive for this organism. Unfortunately no agglutination tests were carried out on the serum. However, typical lesions in rabbits were produced when the organisms were injected subcutaneously.

CASE 3. A 32 year old white soldier complained of "sore throats" and "stuffing of the nose and ears" for 6 months. Palliative treatment was of no avail and a month later he reappeared with history of pain in the left upper jaw. A dark left maxillary sinus was observed on transillumination. The patient was afebrile. Routine laboratory examination of blood and urine was normal. Antral irrigation washed out a foul smelling pus. Bacteriologic investigation proved the organism to be *B. necrophorum*. The soldier had not been exposed to animals. Activated zinc peroxide and iodides were without effect. Penicillin, locally and parenterally were used. A Caldwell-Luc operation was performed about 6 weeks after admission. Patient made an uneventful recovery. Due to technical difficulties we were unable to do serologic examination for the organism. Rabbit inoculations of the cultured organism produced characteristic lesions described by Orcutt.<sup>4</sup>

**Summary and Conclusion.** 1. The importance of routine anaerobic as well as aerobic bacteriologic techniques has been stressed.

2. Three cases of infection with *B. necrophorum* are presented. All recovered. No history of exposure to domestic animals was obtained.

We wish to express our appreciation to Capt. J. H. Hersh, M.C., and to Dr. A. E. Evans for permission to use some of the clinical material presented.

#### REFERENCES

1. BUHLER, V. B., SEELY, C. W., and DIXON, D. D.: Am. J. Clin. Path., 12, 380, 1942.
2. CUNNINGHAM, J. S.: Arch. Path., 9, 843, 1930.
3. DACK, G. M., DRAGSTEDT, L. R., JOHNSON, R., and McCULLOUGH, F.: J. Infec. Dis., 67, 169, 1938.
4. ORCUTT, M. L.: J. Bact., 20, 343, 1930.
5. SHAW, F. W., and BIGGER, I. A.: J. Am. Med. Assn., 103, 688, 1934.

## UNILATERAL DIAPHRAGMATIC FLUTTER

BY RAYMOND HARRIS, M.D.

AND

DAVID SCHERF, M.D., F.A.C.P.

FLOWER AND FIFTH AVENUE HOSPITALS, NEW YORK

(From the New York Medical College, Metropolitan Hospital Service)

DISTURBANCES of diaphragmatic motility fall into several categories. One group, characterized by clonic contractions of the diaphragm, includes singultus and is the most common of all. Another group, less common than the first, is produced by tonic contractions of the diaphragm and occurs in tetany, tetanus, and hysteria. Under these conditions dyspnea as well as pain near the attachment of the diaphragm to the ribs may be found. A third group in which abnormal, irregular contractions of the diaphragm are seen is occasionally observed in tics and chorea.

In a particularly rare form the whole diaphragm or parts of it contract at a rapid rate causing the appearance of special symptoms and signs which enable the clinician to make the diagnosis often without resort to laboratory facilities. We had the opportunity to observe an example which presented unusual features.

**Case Report.** S. P., 84 year old male, was admitted November 11, 1944, complaining of headache, vertigo, and occasional chest pain. Rarely ill, he began to experience dizzy spells in 1943; no loss of consciousness occurred at any time. Almost simultaneously the patient began to suffer from headaches. In 1944 the patient had a slight attack of "influenza." Six weeks before admission to the hospital spells of vomiting occurred. For the past 5 years he had complained of cough and had expectorated white mucus which was occasionally blood-tinged. He was accustomed to sleep on 3 pillows at home and also reported some exertional dyspnea. He was confined to bed for a few months prior to admission because he felt too weak to walk. The patient was a heavy smoker. Until 11 years before admission he had worked in a paint factory mixing lead pigments.

On admission the temperature was  $37^{\circ}\text{C}$ ., pulse rate 70, and respiratory rate 20. The emaciated, slightly dehydrated patient lay quietly in bed in no acute distress. He was oriented as to time and place, but responded slowly to questions. Examination of head, eyes, ears, nose, and throat was essentially negative. The chest was markedly emphysematous with flaring of the lower ribs. Breathing was mainly abdominal. No thrills or pulsations were felt or seen in the anterior or posterior chest wall. Percussion and auscultation of the lungs revealed the typical findings of an advanced emphysema. Percussion of the heart was rendered uninformative by the emphysema. The heart sounds were distant and rhythmic. No murmurs were heard. The blood pressure was 140/80 mm. Hg. At the base of the heart the cardiac sounds were so faint as to be almost inaudible.

In the lower right chest peculiar rapid sounds varying in intensity from time to time were heard. These sounds usually were louder, clearer, shorter, and higher pitched than the heart sounds. The fast rate and the absence of any accentuation made these sounds resemble fetal heart sounds (embryocardia). Despite the high rate it was always possible to count them because each examiner instinctively counted in the same manner as he would count the heart beat, 2 beats constituting 1 cycle. In this way it was found during an observation period lasting 16 weeks that the rate varied between 250 and

300 beats per minute with the average rate being 270 beats per minute. The point of maximum intensity of these sounds was located in the fifth and sixth right interspaces just lateral to the mid-clavicular line. These sounds were also heard posteriorly from the inferior angle of the right scapula to the base of the lung. Slightly louder on expiration, they seemed superficial as if they were coming from just below the chest surface. The sounds were not heard in the left chest at all. They were present during all phases of respiration as well as when the patient stopped breathing.

Inspection of the abdominal wall showed, on one occasion only, slight rapid fluttering movements in the right upper quadrant just below the border of the ribs. Over the abdomen the flutter sounds were not audible and all physical findings were negative.

Neurological examination was essentially normal.

Laboratory data were not remarkable; only a few of the findings will be recorded. Red blood cells, 4 million; hemoglobin, 13 gm. per 100 cc.; leucocyte and differential counts were normal. The urine revealed 1+ albumin, with few red blood cells, epithelial cells, and no casts. Blood sugar was 78 mg. per 100 cc.; urea nitrogen 12.5 mg. per 100 cc. Blood Wassermann and Kahn tests were negative. Sedimentation rate (Westergren) was 11 mm. in 15 minutes and 22 mm. in an hour. Blood calcium was 10.7 mg. per 100 cc. Venous pressure was 65 mm. All other findings were also in the range of normal values.

Following the discovery of the abnormal sounds the patient was further questioned and he related that he had been aware of "something going up and down like a clock all the time" in the right chest at the level of the right diaphragm. He had experienced this sensation for the first time about a month before admission to the hospital. He added that there was some pain in this area; since the distress was worse at night, it interfered with his sleep. After a few weeks in the hospital this pain disappeared as did the clock-like sensation. The abnormal sounds, however, were audible as ever to the examiners.

The abnormal sounds were heard regularly up to November 28 when they became less constant and were occasionally missed. When absent, the sounds could always be restored by having the patient cough or breathe deeply.

Figure 1 shows that the rate of the abnormal sounds bore no apparent relationship to the heart rate or to the respiratory rate. Coughing made the sounds louder and faster. On the several occasions that the patient was examined during sleep the abnormal sounds were never heard.

The electrocardiogram showed a regular sinus rhythm without evidence of myocardial damage. Using silver electrodes and needles placed subcutaneously in different locations around the area where the sounds were most audible, we tried to register some abnormal activity of the diaphragm, but all attempts failed.

Roentgenograms revealed a prominent aortic knob with evidence of calcification of the aorta. The heart was normal in size and shape. The lungs showed evidence of emphysema and increased markings. An old healed fracture of the left tenth rib posteriorly was found. Several kymographic, roentgenographic, and fluoroscopic examinations of the diaphragm with the patient standing as well as in the lateral position were carefully made, but these failed to show any abnormal movements. Skull plates were negative.

Twice the right phrenic nerve was blocked successfully by novocaine. During the first attempt the abnormal sounds persisted for 15 minutes after fluoroscopy indicated paralysis of the right diaphragm. Then they disappeared only to return immediately by having the patient cough. In the second attempt the abnormal sounds persisted during the entire period that the right diaphragm was paralyzed. This time, however, small rapid flutter movements were visualized under the fluoroscope in the lateral half of the otherwise stationary right diaphragm.

Electroencephalograms showed normal brain patterns.

The recording of the abnormal sounds (Fig. 2A) taken from the sixth right interspace in the right axillary line revealed rapid regular beats with a rate of

272 per minute. The heart sounds were registered immediately thereafter but the pulmonary emphysema made the registration difficult. Figure 2B shows the stethogram of the heart sounds obtained from the fifth left intercostal space and left mid-clavicular line where the cardiac sounds were heard best.

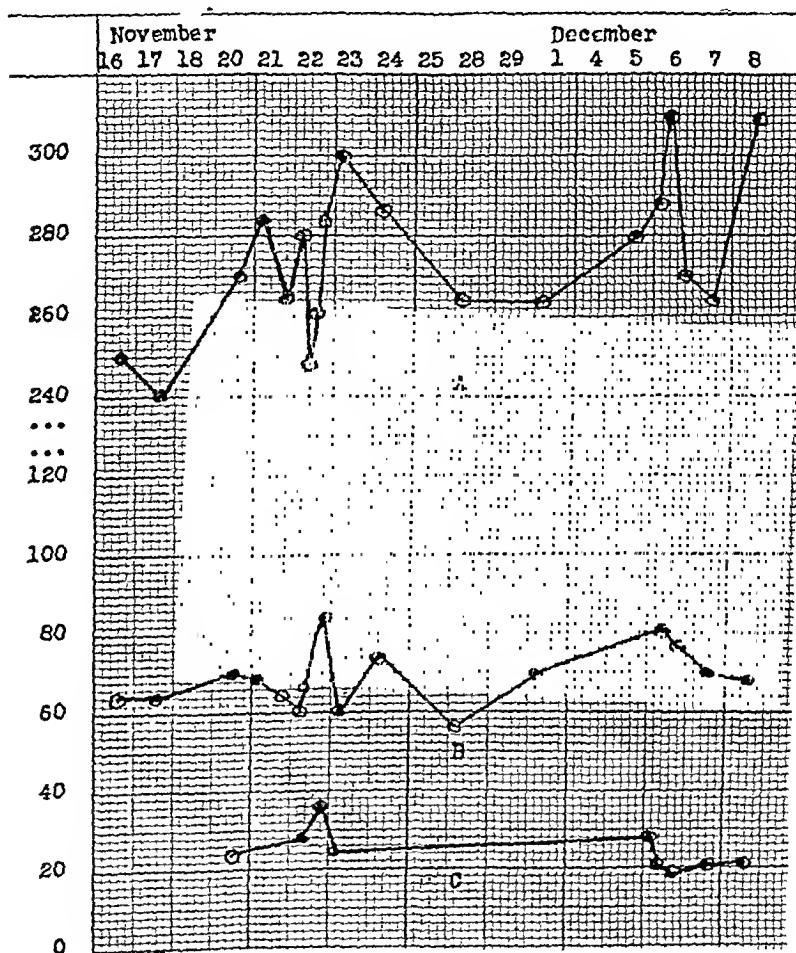


FIG. 1.—No relation is visible between the rate of the heart (B) or the respiration (C) and the rate of the abnormal sounds in the chest (A).

Quinidine sulfate, 3 grains every 2 hours for 26 doses, was given. Under this régime the abnormal chest sounds disappeared, but could be elicited again by coughing or deep breathing. Whereas previously these sounds, if produced by these maneuvers, would last for a considerable time, they now remained only for a few seconds. This effect disappeared a few days after quinidine was discontinued. The patient was dismissed after an observation period of 16 weeks, during which the abnormal phenomenon was observed. Occasionally it disappeared; however, it would again reappear for short periods.

**Discussion.** The finding of rhythmic sounds, resembling fetal heart sounds and bearing no relationship to cardiac activity, in the right chest of an 84 year old male is unusual enough to demand recording. Review of the literature on disturbances of diaphragmatic activity

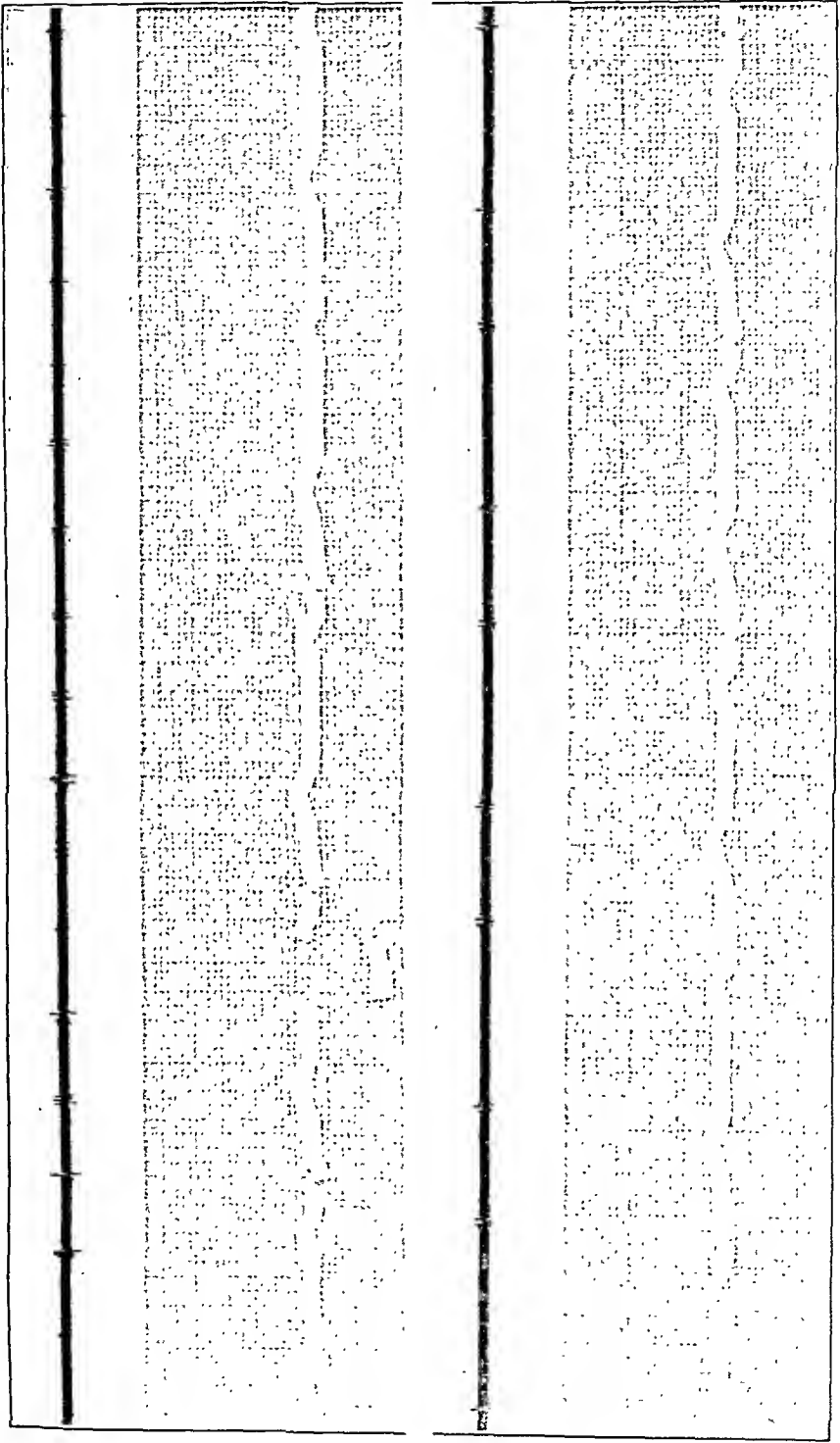


FIG. 2.—A, The stethogram of the abnormal sounds and the electrocardiogram in Lead II. B, The heart sounds registered from the apical area with the electrocardiogram in Lead II.



TABLE 1.—REPORTED CASES OF DIAPHRAGMATIC FLUTTER (Tic)

Author	Year	Sex	Age	Clinical picture	Diagnosis	Rate/min.	Fluoroscopy	Etiology	Treatment	Result	Miscellaneous
Gamble <i>et al.</i> <sup>1</sup>	1925	M	38	Dyspnea, pain in left arm; small, rapid bilat. thor. excursions; pres. asleep	Postencephalitic tic of diaphragm.	84	Abnor. bilat. spasmodic contr. of d.	Encephalitis	Ethyl chloride spray	Temp. relief	
Downum <sup>2</sup>	1927	F	67	Sharp precord. pain, intercostal pain; rapid, pure abd. resp.; "fluttering of heart"; intermittent attacks lasting 1 hr. and longer	Postencephalitic diaphragmatic tic	90-130	Bilat. flutter of d.	Encephalitis	Freezing and section of phrenic	Cured	
Skullern <sup>10</sup>	1931	F	37	Harassing attacks of rapid resp. lasting a few min.; spasm of facial muscles; rapid, shallow, bilat. chest movements	Postencephalitic diaphragmatic tic	200	Bilat. flutter of d.	Encephalitis	Bilateral phrenicectomy	Cured	Entire relief not obtained until complete ablation of thor. segment of r. phrenic through chest done
Smith <sup>11</sup>	1932	F	20	Jerky breathing with hiccoughs; marked resp. grunts; absent during sleep	Diaphragmatic tic	100-140	Right d. more involved; rapid flutter	Following appendectomy	Sect. of r. interl. phrenics	Phenomenon temp. disappeared	
Smith <sup>11</sup>	1932	F	21	Rapid, jerking, grunting, spasmodic resp.; absent during sleep	Diaphragmatic tic	120	Tic of r. and l. d.	Encephalitis	Sect. of r. phrenic	Impr'd for 3 mos.	
Porter <sup>8</sup>	1936	M	57	Angular-liko pain; jerky resp.; reg. abnor. bilat. chest sounds	Diaphragmatic flutter	250+	Bilat. flutter of d.	(See Misc.)	Phrenic block with novocaine	Temp. relief	Later reported by 2 other writers as a possible hysteria in psychopathic inf. male; they tried bilat. phrenicotomy with only temporary relief <sup>12,13</sup>
Handron <sup>4</sup>	1941	F	36	Sev. up abd. pain related to meals; bilat. vibration of up. half of body; pain l. shoulder; occ. vom.; splashing sounds in abd.; resp. grunts; attacks intermittent	Diaphragmatic tic	128	Bilat. clonic contr. of d.	Vol. pyloric stenosis operation	Resection of both phrenics	App. cured	Patient had repeated intestinal obstructions

reveals only 1 case that is at all similar. First described in 1936 by Porter, this same case has been reported several times as the patient traveled from one hospital to another giving different histories each time.<sup>5,9,12</sup> That patient, 57 years old when first described in 1936, complained of angina-like pain. Abnormal sounds independent of cardiac activity could be heard over the entire lower third of the chest anteriorly and posteriorly with a rate of 250 to 300 beats per minute. Registration of these sounds was possible. Fluoroscopy revealed bilateral symmetrical flutter movements of the diaphragm.

The individual reported in this article is definitely not the same one described in previous papers. In this case the sounds were caused by the rapid contractions of one part of the right diaphragm which showed normal respiratory movements. No case of this type seems to have been reported. It is interesting to note that the rate and character of the abnormal sounds were similar in both cases. In our patient these sounds were heard only over a circumscribed area and fluoroscopy revealed normal respiratory movements of the diaphragm. Only following block of the right phrenic nerve with paralysis of the right diaphragm could fluttering movements be seen in one small area of the right diaphragm corresponding to the point of maximum intensity of the abnormal sounds. Blocking of the phrenic nerve in this case did not stop the phenomenon.

In Table 1 are listed 7 cases, including the observation reported by Porter, in which the rate of the diaphragmatic contractions was rapid (over 80 per minute) and the clinical data were complete. No attempt is made here to list cases of diaphragmatic disturbances which do not fulfil the above two requirements. In none of these cases with the exception of Porter's were abnormal chest sounds caused by abnormal contractions of the diaphragm heard. These disturbances followed encephalitis or appeared after an abdominal operation. It is worth while to note that in these cases block or section of the phrenic nerves repeatedly led to immediate disappearance of the abnormal diaphragmatic contractions.

The appearance of painful sensations with abnormal contractions of the diaphragm, as was found also in our case, is known, easily explained, and does not require further comment.

Most of the reported cases have followed some form of encephalitis and produced such respiratory distress that surgical operation on the phrenic nerves with varying success had to be done.

It seems that there are several mechanisms through which this condition may occur. (1) In cases in which this phenomenon results—encephalitis and perhaps from hysteria, abnormal central stimuli coming down the phrenic nerve from the brain may cause rapid contractions of the diaphragm. (2) Abnormally fast contractions of the diaphragm may be observed displaying the rhythm and rate of the heart of the individual. This is not at all rare in experiments on dogs in which the left half of the diaphragm occasionally contracts rhythmically with the heart. One of us often saw these unusual contractions in the dog disappear immediately if the left phrenic nerve were removed

from the heart or severed caudad from the heart before it reached the diaphragm. The potentials due to cardiac activity produce enough stimuli to cause contractions of the diaphragm. Under normal conditions these stimuli are not strong enough, but apparently suffice if the sensitivity of the diaphragm is altered during an experiment by anesthesia, exposure, or drugs. (3) It also seems certain that pathologic changes as found in diaphragmatic pleurisy (particularly following pulmonary infarctions) or in peritonitis also lead to abnormal contractions of the diaphragm. Pathologic changes in the diaphragmatic muscle are very common in these various conditions.<sup>7</sup>

In the case reported here, the assumption seems justified that we are dealing with a purely peripheral disturbance. Successful blocking of the phrenic nerve did not abolish the phenomenon and there was no relationship to cardiac activity. In an attempt to explain the mechanism of the abnormal phenomenon, the comparison with attacks of paroxysmal tachycardia of the heart is obvious. From animal experiments it is known that stimulation of heart muscle whose metabolic state has been altered through some sort of damage (as anemia) may lead under certain circumstances to a long series of rapid abnormal contractions (paroxysmal tachycardia, flutter, or fibrillation).<sup>1,2</sup> This happens particularly if the stimulus is applied in a certain early phase of diastole called the "vulnerable phase."<sup>13</sup> It is possible that a similar mechanism existed in a small part of our patient's diaphragm. In favor of this explanation is the fact that once the phenomenon disappeared, it could always be brought back by cough or deep respiration, that is, by renewed stimulation of the injured diaphragmatic muscle. It was always present when the patient breathed deeply and was absent when the patient was asleep, that is, during more superficial breathing. Accordingly we may be dealing with an abnormal response of a small part of the diaphragm to physiological stimuli. Porter's case with the symmetrical fluttering of both halves of the diaphragm cannot be explained in this way.

With regard to the viewpoint expressed by Lewis and Dock<sup>8</sup> that the contraction of the heart muscle does not contribute to the origin of the first heart sound, the appearance of loud sounds caused by contraction of a part of the diaphragm in our case is of particular interest. These sounds need, however, not be attributed to muscular contractions alone. Vibrations due to stretching of connective tissue in tendinous parts of the diaphragm may be responsible.

**Conclusion.** A case of unilateral diaphragmatic flutter in an 84-year-old man is reported, and recorded, in which rapid loud rhythmic sounds in the right chest independent of the heart sounds led to the clinical diagnosis. These sounds were caused by contractions of a part of the right diaphragm.

**ADDENDUM:** The patient was reexamined on June 13, 1945, and October 4, 1945. He stated that he had occasional recurrence of the clock-like sensations in the right chest. No abnormal sounds were heard during normal respiration or after coughing on both occasions.

## REFERENCES

1. ANDRUS, E. C., and CARTER, E. P.: The Refractory Period of the Normally-beating Dog's Auricle, *J. Exp. Med.*, **51**, 357, 1930.
2. DE BOER, S.: Herzwühlen, Flimmern, Flattern, gehäufte Extrasystolie, paroxysmale Tachykardie, *Arch. f. d. ges. Physiol.*, **187**, 193, 1921.
3. DOWMAN, C. E.: Relief of Diaphragmatic Tic, Following Encephalitis, by Section of Phrenic Nerves, *J. Am. Med. Assn.*, **88**, 95, 1927.
4. GAMBLE, C. J., PEPPER, O. H. P., and MULLER, G. P.: Postencephalitic Tic of the Diaphragm: Pulmonary Overventilation, and Relief by Blockade of Phrenic Nerves, *J. Am. Med. Assn.*, **85**, 1485, 1925.
5. GOODMAN, M. J.: Paroxysmal Flutter of the Diaphragm Simulating Coronary Occlusion, *J. Am. Med. Assn.*, **116**, 1635, 1941.
6. HANDRON, C. J.: Diaphragmatic Tic, *Ann. Int. Med.*, **14**, 1909, 1941.
7. HITZENBERGER, K.: Das Zwerchfell im gesunden und kranken Zustand, Wien, Springer, 1927.
8. LEWIS, J. K., and DOCK, W.: The Origin of Heart Sounds and Their Variations in Myocardial Disease, *J. Am. Med. Assn.*, **110**, 271, 1938.
9. PORTER, W. B.: Diaphragmatic Flutter With Symptoms of Angina Pectoris, *J. Am. Med. Assn.*, **106**, 992, 1936.
10. SKILLERN, P. G.: Tic of Diaphragm (Postencephalitic) Relieved by Resection of Phrenic Nerves, *J. Am. Med. Assn.*, **96**, 2098, 1931.
11. SMITH, H.: Diaphragmatic Tic Relieved by Section of Phrenic Nerves, *AM. J. MED. SCI.*, **183**, 837, 1932.
12. WHITEHEAD, R. W., BURNETT, C. T., and LAGEN, J. B.: Diaphragmatic Flutter With Symptoms Suggesting Angina Pectoris, *J. Am. Med. Assn.*, **112**, 1237, 1939.
13. WIGGERS, C. J., and WÉGRIA, R.: Ventricular Fibrillation Due to Single, Localized Induction and Condenser Shocks Applied During the Vulnerable Phase of Ventricular Systole, *Am. J. Physiol.*, **128**, 500, 1940.

## INTESTINAL LIPODYSTROPHY (LIPOPHAGIA GRANULOMATOSIS OR WHIPPLE'S DISEASE)

BY HARVEY J. AMSTERDAM, M.D.

AND

DAVID M. GRAYZEL, M.D., PH.D.

THE JEWISH HOSPITAL, BROOKLYN 16, NEW YORK.

(From the Department of Laboratories)

PATIENTS who present as their major complaint, diarrhea, either chronic or of short term duration, usually receive intensive study in order to establish an etiologic (or anatomic) diagnosis. However, many cases of chronic diarrhea are diagnosed incorrectly or signed out with a diagnosis wanting. We wish to report a case of intestinal lipodystrophy (lipophagia granulomatosis or Whipple's disease) as it is the 14th such case to be reported and with the hope that another cause for chronic diarrhea might be further established.

Since Whipple's<sup>12</sup> first description of intestinal lipodystrophy there have been 12 cases reported in the literature. This disease occurs predominantly in males usually between the 4th and 6th decade. Among the major complaints are diarrhea with or without blood, sometimes steatorrhea, postprandial discomfort and distention, asthenia and weight loss. They usually further present a moderate anemia, normal leukocyte and differential counts, hypotension, skin pigmentation and achlorhydria. Necropsy findings are consistent. These show a mesenteric lymphadenopathy with lipid replacement

of these lymph nodes, and enlarged intestinal villi with characteristic fat-laden cells in the mucosa and submucosa.

In no case, including our own, was the diagnosis of intestinal lipodystrophy made antemortem. The most frequently entertained antemortem diagnosis have been, regional ileitis, ulcerative colitis, sprue, Boeck's sarcoid and Hodgkin's disease. Table 1 presents all the cases reported to date in a form which we have slightly modified from the paper of Apperly and Copley.<sup>1</sup> It is worth mentioning that in 3 cases, Whipple,<sup>12</sup> Apperly and Copley<sup>1</sup> and our own, an exploratory laparotomy was performed during the course of the illness and Hodgkin's disease or sarcoma, Hodgkin's disease, and questionable tuberculosis, were respectively reported from mesenteric lymph node microscopy.

TABLE 1

	Whipple	Blumgart	Blumgart	Blumgart	Fleischman	Jarcho	Boeck	Korsch	Hill	Rheinhart	Sailer	Copley and Apperly	Vaux	Amsterdam and Grayzel
Sex . . . . .	M	M	F	M	M	M	M	M	M	M	M	M	M	M
Age . . . . .	36	42	44	32	38	37	45	60	60	74	45	51	49	54
History, time in yrs. . . . .	5	2	2	1½	1	15	1	10	2	1	5	4	9?	2
Post. prand. discom. and disten. . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Asthenia and weight loss . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Diarrhea . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Diarrhea with blood . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Steatorrhea . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fever . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
History of arthritis . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin pigmentation . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin pigmentation, icterus sit. . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Edema, moderate . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Anemia, moderate . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukocytosis . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Eosinophilia . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Low blood pressure . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Achlorhydria . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Terminal acidosis . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Terminal tetany . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
<i>Autopsy Findings</i>														
Pericarditis, fibrous . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocarditis . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleuritis . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peritonitis . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemorrhages . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Enl. intest. villi with fat cells . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesenteric lymphadenopathy . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chylous ascites . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic fibrosis, moderate . . . . .	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+ and 0 indicate presence or absence of symptom or sign.

Blank space—symptom not recorded.

\* Examination of thorax not permitted.

**Case Report.** L. K. (278817), a Jewish white man, age 54, was admitted to the Jewish Hospital of Brooklyn on October 26, 1944, complaining of diarrhea, abdominal distention and loss of weight.

In 1942 the patient was admitted to another hospital complaining of diarrhea of 3 weeks' duration. Following an intensive study an exploratory laparotomy was performed and revealed "firm whitish adhesions of the lower small intestines, with a few whitish areas, and numerous soft nodes along the aorta and spine." Microscopic examination of the areas and nodes were reported as "(1) chronic peritonitis of the ileum, (2) chronic lymphadenitis, probably tuberculous, (3) possibly healed regional ileitis." He was readmitted several times to the same hospital with exacerbations of his symptoms. In August, 1943 progressive pigmentation was noted on both lower extremities. Roentgen ray studies of the gastro-intestinal tract were interpreted as showing a deficiency pattern. In April, 1943 he was admitted to another hospital where

a gastro-intestinal study was made which proved negative. He was maintained on a high vitamin, low fat diet.

Five days prior to his admission to this hospital diarrhea began again, unassociated with pain. Daily postprandial distention was noted for about 3 hours, and a fever of 100° to 101° F. was recorded for the 6 weeks prior to admission. His stools were described as brown, liquid, not foamy or foul-smelling, and no melena was noted. He felt weak and listless. There was no history of arthritis.

On admission the patient was a pale, thin, emaciated white man with a dry scaly skin and a markedly distended abdomen. The blood pressure on several occasions ranged from 82 to 110 systolic and from 40 to 68 diastolic. The lungs were clear to auscultation and percussion and an apical systolic murmur was heard. The abdominal wall was slightly edematous. Peristalsis was visible and auscultation revealed normal peristaltic sounds. Rectal examination was negative. Peripheral edema was slight.

Almost throughout his hospital stay his temperature ranged between 100° and 102° F. Several Roentgen ray studies of the gastro-intestinal tract were interpreted as representing a deficiency pattern. Guinea pig inoculation of the stool failed as the animal died prematurely of secondary infection. The radiology department ventured a Roentgen ray diagnosis of regional ileitis principally involving the terminal ileum, as the ileal coils appeared narrowed and had serrated borders. Roentgen ray examinations of both hands were negative. Urine analysis on several occasions revealed specific gravities ranging from 1.002 to 1.010 with traces of albumin but no sugar. Blood counts showed hemoglobins ranging from 48 to 67% with red blood counts ranging from 2.19 to 3.28 million per c.mm. A typical blood count read: hemoglobin 50%, R.B.C. 2.88, W.B.C. 6,450, polymorphonuclears 72, bands 8, lymphocytes 15, monocytes 5, eosinophils 0. The sedimentation rates were 27 and 40 mm. per hr. and the stools consistently showed 1 to 4+ blood, with no ova or parasites found. The total blood protein ranged from 3.17 to 5.3 mg. % with from 2.9 to 3.1 mg. % globulin, and 1.0 to 1.3 mg. % albumin with an A/G ratio of from 2.2 to 3.1. The blood urea nitrogen, CO<sub>2</sub> combining power, uric acid, calcium and cholesterol values were within normal limits. Blood agglutination for the typhoid-Salmonella group was negative. A tuberculin test was negative in 1:100,000 dilution.

Despite a great deal of parenteral therapy including whole blood transfusions, amino acids, glucose and vitamins, he continued to go downhill. His diarrhea continued and abdominal distention was always present. Toward the end he had several bouts of melena and died on December 19, 1944 on his 55th hospital day.

*Necropsy.* The body was that of an emaciated white man weighing 40 kg. The peritoneal surfaces were dull and the mesentery was thickened and studded with easily palpable, firm lymph nodes. The heart weighed 220 gm. and was grossly not unusual. The lungs showed no evidence of tuberculosis; the right and left lungs weighed 300 and 340 gm. respectively. Their cut surfaces were not unusual. The tracheobronchial lymph nodes were likewise not unusual. The jejunum presented a thickening of the valvulae conniventes. The mucosa was purple-red in color, and between the thickened valvulae the mucosa had a velvety appearance. The proximal ileum presented a similar picture, but the terminal ileum was thickened. The serosa of the terminal ileum was covered with occasional white, flat, plaques measuring up to 1.4 x 0.9 cm. These areas were firmer than the surrounding tissue. The mucosa of the terminal ileum presented ulcerations underlying the white plaques described. The mesentery was markedly thickened and studded with lymph nodes measuring up to 1.2 x 1 x 1 cm. They were firm, grey-white in color and not matted together. On section, they were gray-white but no cystlike spaces were seen. The liver weighed 1210 gm., and its external surface was red brown in color. On section the cut surface showed a nutmeg appearance. The pancreas weighed 52 gm. and was yellow-tan, and on section showed the normal lobular pattern. The suprarenal glands together weighed 17 gm. and

were grossly not unusual. The right and left kidneys weighed 155 and 185 gm. respectively. The capsules stripped with ease and the external surfaces were red-brown and glistening. On section the cut surfaces bulged; the cortex was easily demarcated from the medulla. The spleen, musculo-skeletal system, and bone marrow were not unusual.

*Microscopic.* Aside from the gastro-intestinal tract and mesenteric lymph nodes there was nothing of note. The pancreas showed no fibrosis.

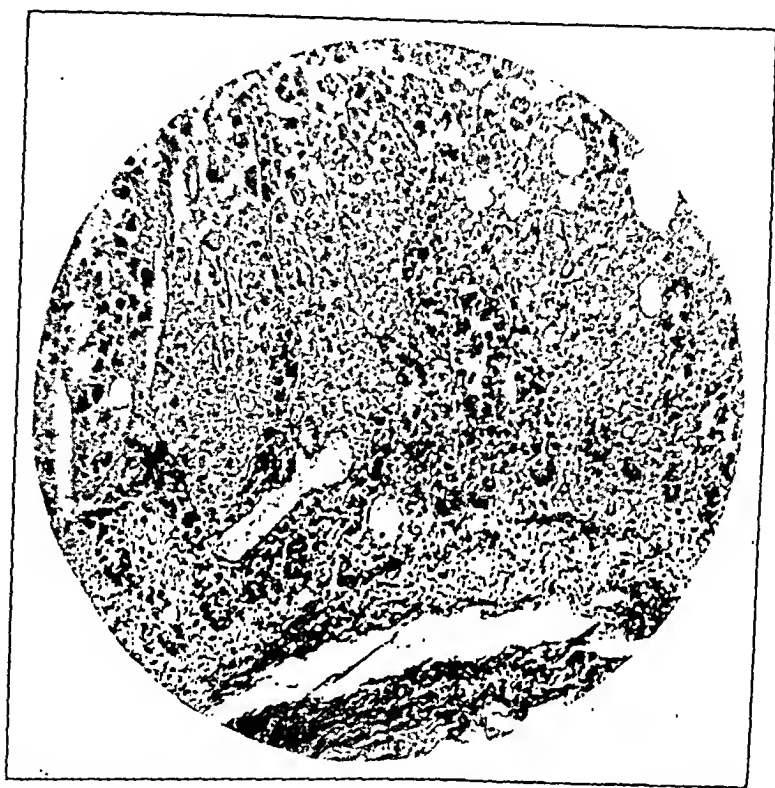


FIG. 1.—Photomicrograph of jejunum showing foam cells in the lamina propria. H. and E.  $\times 100$ .

In preparations from the jejunum (Fig. 1) the villi were prominent and blunted. In many places the entire mucosa was ragged and necrotic. Crypts found in the mucosa were few in number and were greatly distorted. Large, foamy, mononucleated cells were seen in the mucosa, some of these cells lying within thin-walled endothelial-lined spaces. In some areas these foamy macrophages comprised the most prominent cell seen. In no place were giant cells seen. The remainder of jejunal coats were not unusual. In preparations from the terminal ileum the villi were decidedly blunted and the mucosa here also showed a marked necrosis. However, there were no large foamy cells seen in the mucosa. In preparations from the ileocecal region the mucosal pattern approached a more normal architecture.

In preparations from the mesenteric lymph nodes, under low power the cytoarchitecture was markedly distorted. (Fig. 2.) The glands were composed of numerous thin-walled endothelial-lined spaces presenting an almost swiss-cheese pattern. Even under the low magnification large foamy macrophages could be seen. Under a higher magnification (Fig. 3) these spaces could be seen to be filled with large foamy macrophages with vesicular nuclei. The remainder of the lymph node consisted of nests of foam cells and islands

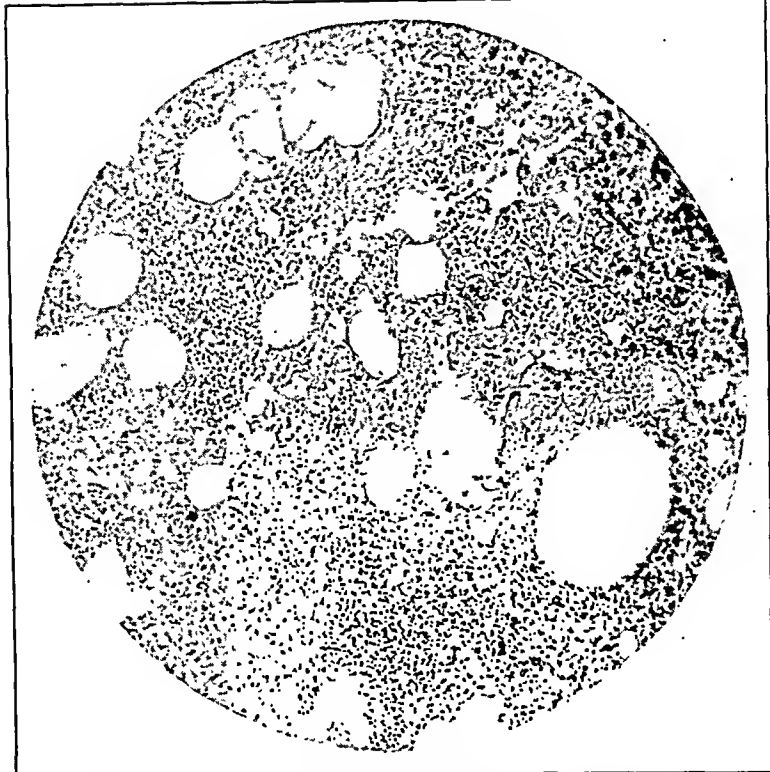


FIG. 2.—Photomicrograph of lymph node showing cystic spaces and foam cells.  
H. and E.  $\times 100$

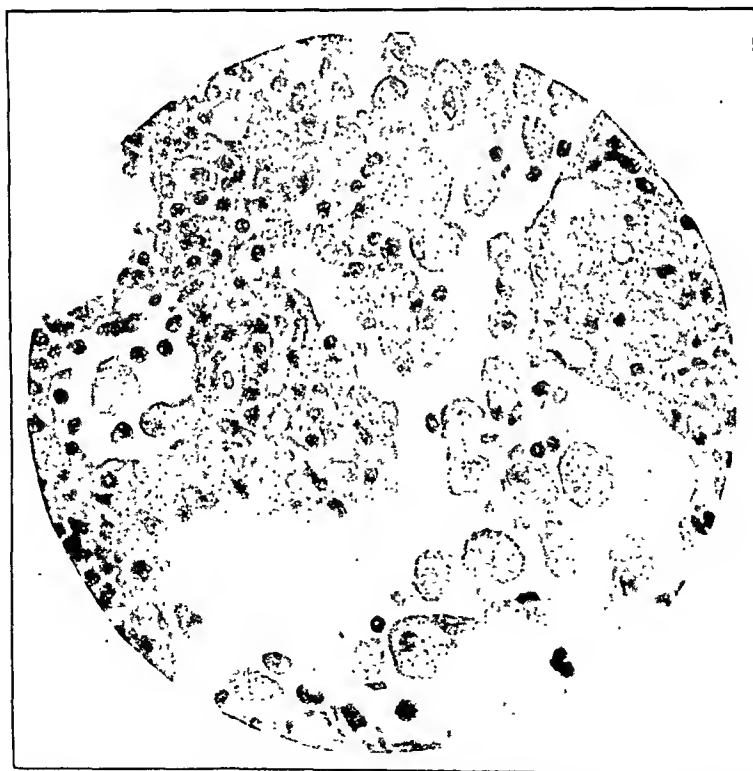


FIG. 3.—Photomicrograph of lymph node showing the foam cells under higher magnification. H. and E.  $\times 400$ .



of lymphoid tissue, and also occasional multinucleated giant cells. In preparations stained with Scharlach R (Fig. 4) these foam cells were seen to contain orange granules. These cytologic characteristics were seen in all of the mesenteric lymph nodes studied.

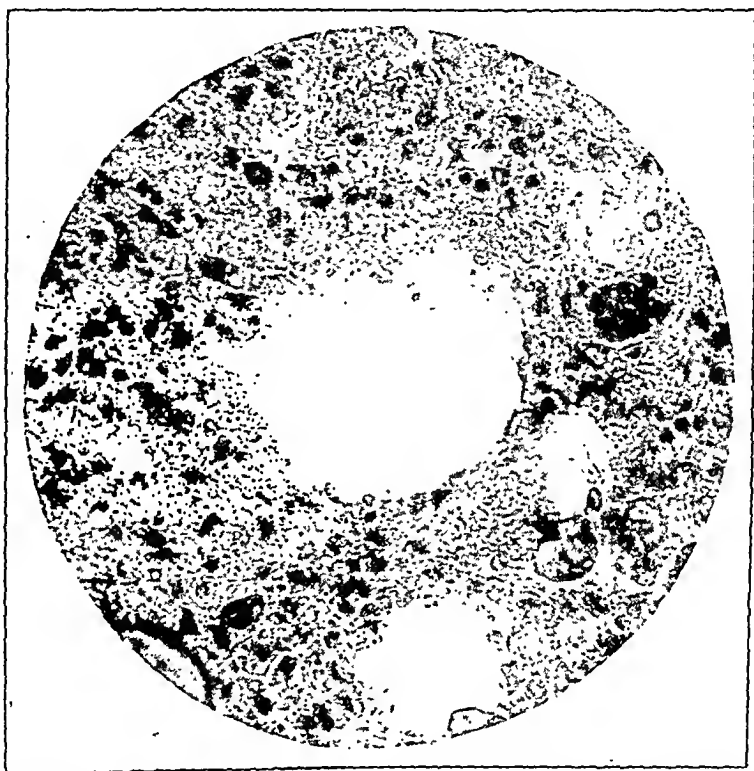


FIG. 4.—Photomicrograph of lymph node showing the large cells filled with fat. Scharlach R.  $\times 400$ .

**Discussion.** The cause and the pathologic physiology involved in intestinal lipodystrophy remains obscure. There are, however, several theories on record to explain the clinical and pathologic findings. Ryle<sup>9</sup> states that chronic fatty diarrhea on a pancreatic basis is overstressed, while disease involving the absorbing mechanism has not received sufficient attention. Blockage of the lacteals with subsequent fatty diarrhea has been reported by a number of investigators.<sup>6,7,9</sup> In no case of intestinal lipodystrophy has obstruction to the thoracic duct or cisterna chyli been found, although such obstruction does lead to chylous ascites and lymph node changes as seen in this disease. Jarcho<sup>7</sup> suggests the possibility of some congenital malformation in the mesenteric lymph nodes as the cause for this disease.

The dilatation of the mesenteric lymph node spaces is the most consistently found lesion in this disease. Hill<sup>6</sup> believes that there is dilatation by chyle with subsequent breakdown of the emulsion and inspissation. Clinically, intestinal lipodystrophy is very similar to the sprue syndrome but the latter does not, or only rarely, presents intestinal changes as seen in Whipple's disease. Fairly and Mackie<sup>4</sup>

report 3 lymphoblastomas which gave rise to a sprue syndrome and believed that malabsorption of food products was the cause for the diarrhea. Blumgart<sup>3</sup> also regards malabsorption as the primary factor. Along similar lines Reinhart<sup>8</sup> believes that there may be an increased excretion of fat into the intestines. And finally the liberation of lipolytic ferments from damaged cells results in fat and fatty acid stasis in lymph nodes. The saponified fats are engulfed by giant cells and eventually there is further chronic inflammation, fibrosis and obstruction.<sup>1,10</sup>

The fever presented by our case could be explained on the constant presence of decubitus ulcers, and occasional phlebitis resulting from almost continuous intravenous therapy.

The diagnosis of intestinal lipodystrophy presents obvious difficulties. However, when more cases are reported, a pattern of symptoms and signs may make it easier. Within the past 8 years, 9 of the 14 cases have been reported; the most recent, by Vaux.<sup>11</sup> The treatment of this disease must remain symptomatic until an etiologic basis is discovered. Parenteral therapy with vitamins, glucose, protein hydrolysates and transfusions offer the most for these patients. Boeck<sup>2</sup> used pancreatin with no success.

**Summary.** 1. A case of intestinal lipodystrophy (lipophagia granulomatosa or Whipple's disease) is presented.

2. The literature is reviewed and the theories for its mechanism and pathologic physiology are presented.

#### REFERENCES

1. APPERLY, F. L., and COPLEY, E. L.: *Gastroenterology*, 1, 461, 1943.
2. BARGEN, J. A., BOLLMAN, J. L., and KEPLER, E. J. (as quoted by Boeck): *Am. J. Digest. Dis. and Nutr.*, 4, 728, 1938.
3. BLUMGART, H. L.: *Arch. Int. Med.*, 32, 113, 1923.
4. FAIRLY, N. H., and MACKIE, F. P.: *Brit. Med. J.*, 1, 375, 1937.
5. HILL, J. M.: *Am. J. Path.*, 13, 267, 1936.
6. HURST, A., WRIGHT, G. P., and RYLE, J. A.: *Guy's Hosp. Rep.*, 91, 25, 1932.
7. JARCHO, S.: *Bull. Johns Hopkins Hosp.*, 59, 275, 1936.
8. REINHART, H. L., and WILSON, S. J.: *Am. J. Path.*, 15, 483, 1939.
9. RYLE, J. A.: *Guy's Hosp. Rep.*, 74, 1, 1924.
10. SAILER, S., and MCGANN, R. J.: *Am. J. Digest. Dis.*, 9, 55, 1942.
11. VAUX, D. M.: *J. Path. and Bact.*, 55, 93, 1943.
12. WHIPPLE, G. H.: *Bull. Johns Hopkins Hosp.*, 18, 382, 1907.

#### STEVENS-JOHNSON SYNDROME

##### (ERUPTIVE FEVER WITH STOMATITIS AND CONJUNCTIVITIS)\*

BY MAJ. SIMON KOVE, M.C., A.U.S.

(From the Medical Service, Bronx Area Station Hospital.  
Bronx 57, New York.)

Two cases of an interesting and uncommon syndrome of an eruptive febrile disease associated with stomatitis and conjunctivitis, originally

\* I wish to thank Major B. Neilson, Chief of the Dental Service, Major H. Simons and 1st Lt. B. Capus, of the Eye, Ear, Nose and Throat Service, for their valuable aid in administering local therapy.

described by Stevens and Johnson,<sup>7</sup> are reported here. These cases were encountered within a 2½ week interval with no history of possible contact with each other.

This syndrome has been referred to, at times, as "erythema multiforme bullosum with involvement of the mucous membranes of the eyes and mouth,"<sup>1</sup> or "erythema exudativum multiforme with ophthalmia and stomatitis."<sup>3</sup> However, because of the characteristic clinical picture, it may well be that we are dealing with a distinct clinical entity. Pending further knowledge concerning the etiologic agent, the term "Stevens-Johnson syndrome" or "eruptive fever with stomatitis and ophthalmia"<sup>4</sup> may be applied. Certainly this syndrome differs from erythema exudativum multiforme which is manifested by a cutaneous eruption, mild constitutional symptoms and only mild, if any, oral and ocular involvement. Murphy<sup>6</sup> has noted that the enanthem rather than the exanthem appears to be the most constant feature of the disease. It has been suggested<sup>4</sup> that the syndrome may be a severe or atypical form of erythema exudativum multiforme (Hebra) and that the name "Hebra" be replaced by "Stevens-Johnson."

The clinical course is characterized by the acute onset of fever and prostration, associated with a cutaneous eruption, a severe membranous stomatitis and a purulent conjunctivitis. The oral lining is usually edematous and covered with numerous vesicles which soon rupture. This is followed by the formation of a thick membranous exudate which then sloughs off. The purulent conjunctivitis is usually severe. Panophthalmitis and either partial or total blindness are frequent complications. A macular-papular or vesicular eruption, which varies in severity in individual cases, may be present. The course usually lasts about 2 to 3 weeks and may be followed by a recurrence.<sup>3</sup> A leukopenia or mild leukocytosis is present. There are no characteristic laboratory findings. No light has been thrown on the etiologic agent. Bacteriologic studies have not been illuminating. Staphylococci or streptococci have been isolated from the lesions<sup>1,4</sup> but these may have been secondary invaders. A case associated with Vincent's infection of the mouth has been reported.<sup>2</sup> No transmissible agent was recovered by Edgar and Syverton<sup>3</sup> following animal inoculation of the vesicular fluid from one of their cases. Biopsy of a skin lesion failed to yield any significant findings.<sup>3</sup>

**Case Reports.** CASE 1. T. K., a 19 year old white male student, was admitted February 6, 1944 from the dispensary of the City College of New York because of a sore mouth of 1 day duration. The soldier had been well until 1 week prior to admission when he began to have a sore throat, for which he took some cough medicine containing "coccillana bark, tolu and menthol." He denied having taken any other drugs. On the day prior to admission his mouth became painful and he noticed "blisters" on his lips and on the lining of his mouth. These symptoms increased in severity, and on reporting to his unit medical officer on the following day he was sent to the station hospital.

The past history was not significant. He had measles, mumps and chicken-pox in childhood. Venereal diseases were denied.

There was no history of familial diseases.

**Physical Examination.** The soldier was alert, coöperative, oriented and not acutely ill. The temperature was 101.2° F. The skin was clear. The

mucosa of the mouth was somewhat edematous, and numerous vesicles, 0.1 to 0.3 cm. in diameter, containing clear fluid, were present over the entire oral lining including the buccal mucosa, tongue, palate and lips. The conjunctivæ were mildly injected. The lungs were clear. The heart sounds were of good quality and no murmurs were heard. The pulse and ventricular rates were 100. The blood pressure was 120/82. The abdomen was soft and the liver and spleen were not palpable. The extremities were not remarkable. No abnormal neurologic signs were present and there was no lymphadenopathy.

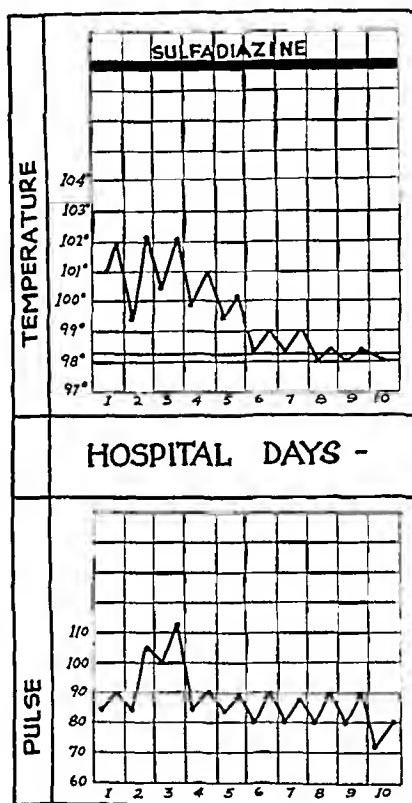


FIG. 1.—Course of Case 1.

*Course.* During the first 2 days following admission the patient became progressively more acutely ill and toxic. The vesicles of the mouth ruptured spontaneously, and a thick grayish membranous exudate formed over the entire lining of the mouth and pharynx. This membrane peeled off easily, leaving angry red areas. The conjunctival injection increased in severity and he began to have a profuse yellowish purulent discharge from both eyes.

On the 3rd day his condition began to improve and he appeared less toxic. At this time the membranous exudate of the mouth began to slough off in plaques of 0.2 to 0.4 cm. in thickness, leaving superficial red areas of ulceration. The patient began to complain of a mild dysuria and, upon examination of the penis, erythema and superficial crusting were noted at the urethral orifice.

The dysuria and external urethritis cleared up completely within 2 days and the purulent ocular discharge began to diminish. Progressive improvement in the general and local conditions continued. By the 10th day the oral membrane had sloughed off and by the 17th day the mucous lining was completely restored. The ocular discharge ceased entirely by the 7th hospital

day. The conjunctival injection, however, subsided more slowly, persisting until the 17th day.

The temperature remained elevated for the first 3 days after admission, ranging between 102° and 102.5° F. It then subsided by lysis and reached a normal level on the 6th hospital day, after which the patient remained completely afebrile.

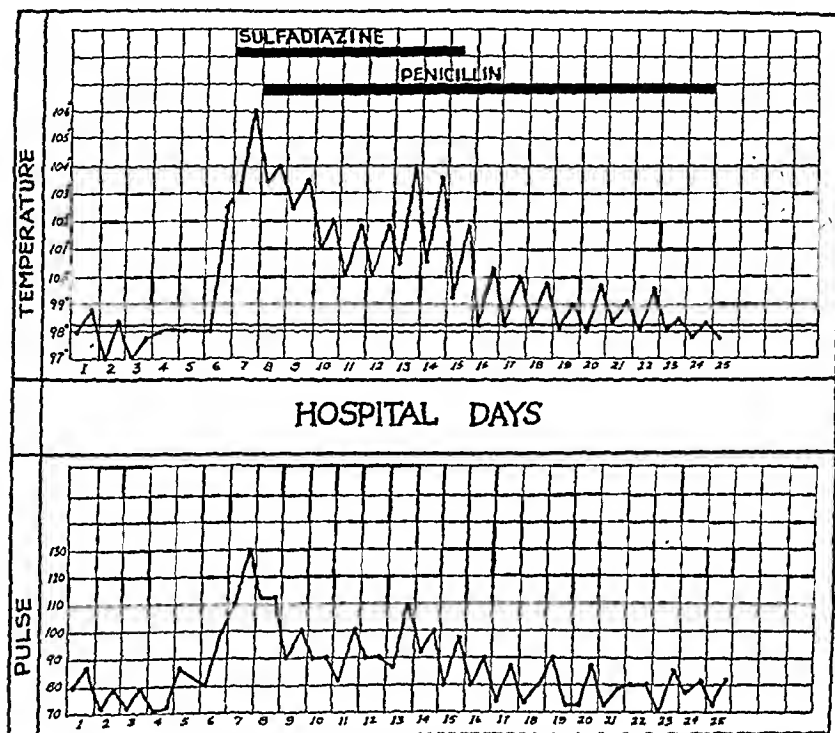


FIG. 2.—Course of Case 2.

Sulfadiazine therapy was started on the 2nd day and continued for 12 days. Six grams were administered daily for the first 4 days and 4 gm. daily for the last 8 days. The mouth was treated with peroxide mouth washes, 2% gentian violet applications and saline mouth irrigations. Under supervision of the Eye, Ear, Nose and Throat Service the eyes were treated with saline irrigations and 5% sodium sulfadiazine eye drops during the acute phase, and thereafter with 0.25% zinc sulphate solution. Vitamins were administered in the form of A and D capsules, thiamine chloride and ascorbic acid.

The patient was discharged on the 26th day in excellent general health. He was completely asymptomatic and no oral or ocular residua were present, with the exception of a somewhat smooth appearing tongue.

*Laboratory Data (CASE 1). Blood Counts:*

Hospital day	W.B.C.	Neutrophils (%)	Lymphocytes (%)	Mono-cytes (%)	Eosino-phils (%)	Baso-phils (%)	Hb. (%)
2nd . . . .	14,200	55	29	11	5	..	90
4th . . . .	8,550	51	28	18	2	1	
6th . . . .	9,550						
8th . . . .	9,550						
10th . . . .	7,300						

Urine examinations and blood cultures were repeatedly negative. Hemolytic streptococcus was the predominating organism on culture of the throat.

The nose and throat culture for Klebs-Loeffler bacilli was negative. A smear of the mouth failed to reveal Vincent's organisms. No fungi were noted upon examination of the oral membrane. The smear of the ocular discharge showed many polymorphonuclear leukocytes but no organisms, and a culture revealed staphylococcus albus. Roentgen ray of the chest was negative. The blood Kahn was negative. Blood agglutinations for typhoid, paratyphoid, tularemia and undulant fever were negative. The Weil-Felix reaction and heterophile antibody test were negative. Determinations, at frequent intervals, of blood sulfadiazine concentration resulted in values which ranged between 5.7 and 8.3 mg. per 100 gm. of free drug.

CASE 2. M. N., a 19 year old white male soldier, was admitted from the infirmary of New York University to the station hospital on February 22, 1944. He had been well until 3 days prior to admission when he began to feel feverish and developed pain and slight swelling below the lobe of the left ear. One day prior to admission 3 gm. of sulfadiazine, in divided doses, were administered by the medical officer of the unit. On the day of admission when the swelling increased in degree, a diagnosis of mumps was made and he was sent to the hospital.

The *past history* was not contributory. He had measles, chickenpox and pneumonia in childhood. There was no history of allergy. About 1 year prior to admission the patient developed a "right submaxillary cellulitis." It was incised and drained, and a sulfonamide drug administered for about 1 week. He denied ever having contracted venereal disease.

The family history was irrelevant.

*Physical Examination.* The soldier was cooperative, alert and not acutely ill. The temperature was 98° F. The skin was warm and dry. A 2-inch well-healed surgical scar was present over the right submaxillary region. A moderate swelling, confined to the parotid gland, was noted below and anterior to the lobe of the left ear. The orifice of the left parotid duct was prominent and erythematous. The lungs were clear. The heart sounds were of good quality and no murmurs were audible. The pulse and ventricular rates were 80. The blood pressure was 126/84. The abdomen was soft and no masses were palpable. The liver and spleen were not felt. The extremities were not remarkable. There was no lymphadenopathy. The neurologic examination was negative. A diagnosis of mumps parotitis was made on admission.

*COURSE.* The patient remained afebrile during the first 5 days following admission. Swelling of the left parotid gland persisted. On the 6th day after admission his temperature rose to 102° F. The palpebral and bulbar conjunctivæ became markedly injected, and a moderate bilateral chemosis and mucopurulent ocular discharge developed. In the evening he began to experience some soreness of the mouth. On the following day the temperature rose to 106° F. and the patient appeared very acutely ill, extremely toxic and prostrated. The entire mucosal lining of the mouth was somewhat edematous. Numerous pearly vesicles were noted on the surface of the tongue. They contained clear fluid and varied in size from 0.2 to 0.5 cm. in diameter. Several irregular areas of thin grayish membranous exudate were present on the surface of the buccal mucosa and the lips. A few small scattered vesicles appeared on the skin; 3 on the palm of the left hand, 3 on the trunk, 4 on the face and 1 on the glans of the penis. They were surrounded by a thin zone of erythema and were 0.2 to 0.4 cm. in diameter. The external urethral orifice was erythematous. Upon specific inquiry the patient admitted having mild dysuria. It was felt at this time that the clinical picture resembled the Stevens-Johnson syndrome with characteristics of an eruptive fever, stomatitis and conjunctivitis. Oral sulfadiazine therapy was started with an initial dose of 4 gm. Thereafter 1 gm. was administered every 4 hours.

On the 8th hospital day he was still acutely ill, although the temperature had dropped to 104° F. The membranous exudate formation and the edema of the oral lining became more marked. The cutaneous vesicles increased in size and slightly in numbers, and a thin membranous exudate appeared at the urethral orifice. Because of the desperate condition of the patient, pen-

icillin therapy (40,000 units administered intramuscularly every 3 hours) was instituted and sulfadiazine was continued. At the suggestion of the dental service, the mouth was treated with topical applications of tyrothricin, containing gramicidin and tyrocidin.



FIG. 3 A

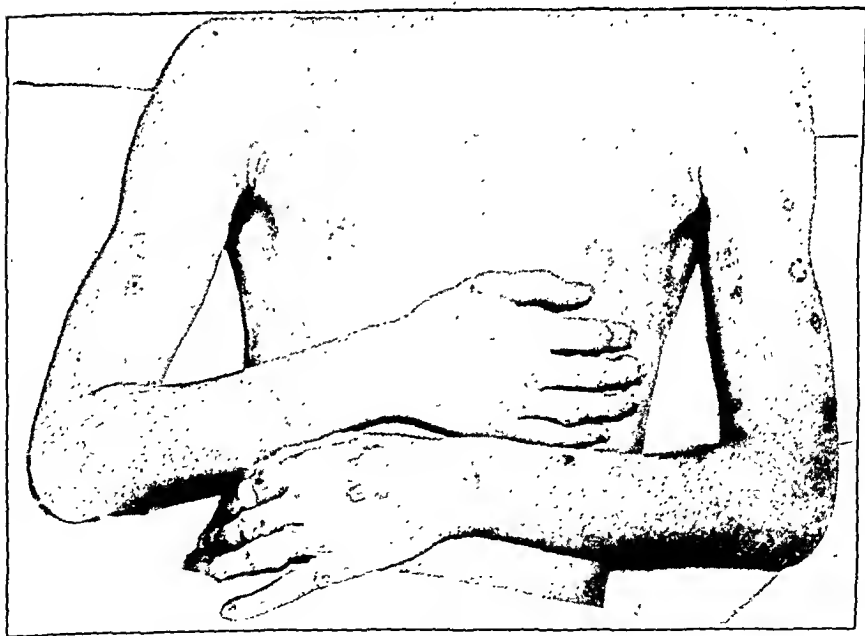


FIG. 3 B

On the 9th day the temperature ran to 103° F. and the patient appeared slightly improved, less toxic and somewhat more alert. The left parotid

swelling had subsided considerably but enlargement and tenderness of the right submaxillary gland became apparent. The ocular chemosis had diminished somewhat. The mouth was less edematous although the membranous exudate on its surface had become more extensive. The cutaneous vesicles increased somewhat in number and were particularly numerous on the hands and wrists. Elsewhere on the body they were few and sparsely distributed. The membranous exudate at the urethral meatus had increased in severity.

During the following 4 days his general condition slowly improved and the temperature gradually subsided to about 101.5° F. The swelling of the left parotid and right submaxillary glands disappeared and the ocular discharge diminished. The cutaneous vesicles of the trunk, face, arms, and forearms began to recede although those of the hands increased in size to form bullæ 0.5 to 2 cm. in diameter. The oral membranous exudate increased progressively. This soon covered the entire lining of the mouth, and thereafter grayish membranous plaques 0.1 to 0.2 cm. in thickness sloughed off slowly. The scrotum became completely covered with vesicles and this was followed by complete desquamation of the superficial epithelium, leaving a raw erythematous surface. Because of difficulty in swallowing and frequent vomiting, the fluid intake was maintained by continuous intravenous infusions.

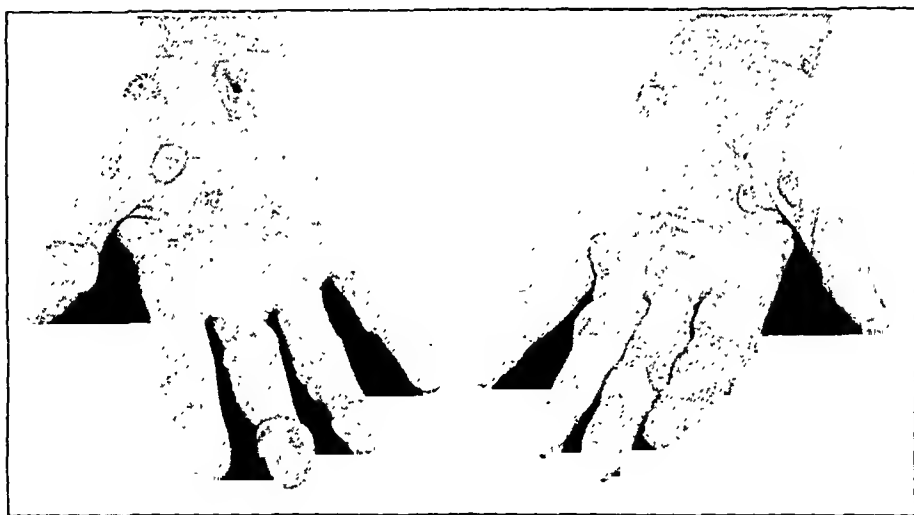


FIG. 3 C

On the 13th day the temperature suddenly rose to 104° F. and the white blood count dropped to 5800, but no change in his general and local conditions were apparent. Because of the possibility of a sulfadiazine reaction, chemotherapy was discontinued. Penicillin therapy, however, was maintained.

The temperature slowly subsided until the 18th day when it reached normal limits and the patient remained afebrile thereafter. The soldier's general condition continued to improve and he began to take food by mouth. Penicillin therapy was decreased to 25,000 units intramuscularly every 3 hours on the 11th day, to 15,000 units every 3 hours on the 19th day and it was discontinued entirely on the 22nd day. A total of 2,700,000 units of penicillin were administered. Thiamine chloride and ascorbic acid were administered subcutaneously during the first 2 weeks. Thereafter they were administered orally, in addition to vitamins A and D, and nicotinic acid.

The skin lesions on the trunk, face, arms, and forearms had dried completely by the 18th day. However, the blebs of the hands increased in size by confluency to several centimeters. This process reached its height at about the 19th day, and thereafter these bullæ dried slowly. The fluid contents



remained clear, although several of these blebs became hemorrhagic on being subjected to trauma. By the 31st day the walls of all the bullæ had completely desquamated, leaving dry erythematous areas at their former sites. The superficial epithelium of the scrotum and glans was restored completely by the 29th day. The membranous exudate of the mouth continued to slough until the 36th day, leaving irregular areas of superficial ulceration which epithelialized rapidly. The lips, which showed considerable fissuring and superficial ulceration and bled with the slightest manipulation, gradually cleared.

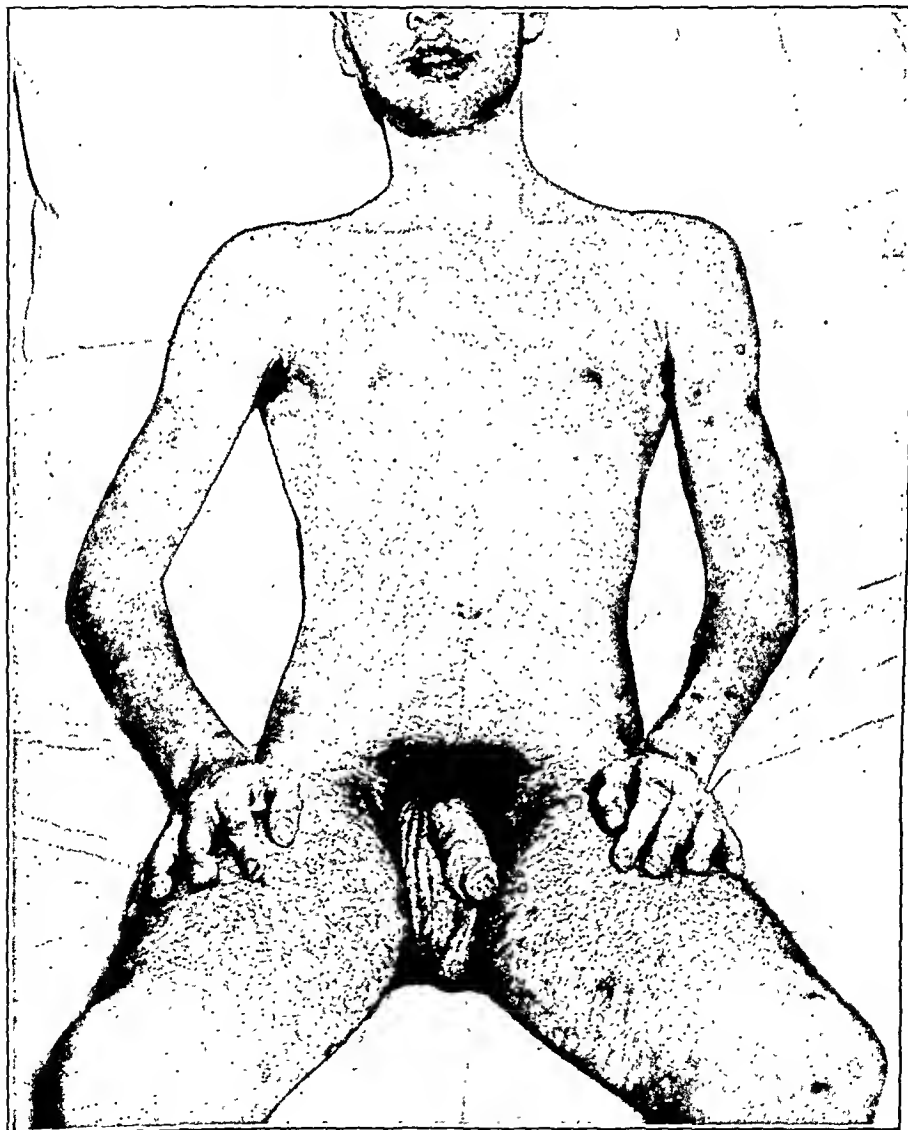


FIG. 3 D

The ocular discharge, chemosis and conjunctival injection began to subside on the 10th day (4 days after onset of the conjunctivitis). On the 14th day adherent membrane on the palpebral conjunctiva bilaterally was noted by

the Eye Service. On the 41st day fine scarring of the conjunctival surfaces of the lids was observed. Two weeks later the Eye, Ear, Nose and Throat Service reported, "Fine scarring of the conjunctival surface of upper lids similar to Stage III trachoma. Symblepharon left lower lid." Mild to moderate bulbar and palpebral injection of the conjunctivæ persisted. No corneal involvement or vitreous opacities were noted at any time. The vision remained unimpaired. Local therapy included 2% aqueous sulfathiazole drops, 1% atropine, boric acid irrigations and compresses to the eyes in the acute stage. Thereafter penicillin ointment (5000 units/oz.), 0.125% neosynephine solution, 0.8% sulfanilamide solution, and 1% silver nitrate solution were employed.

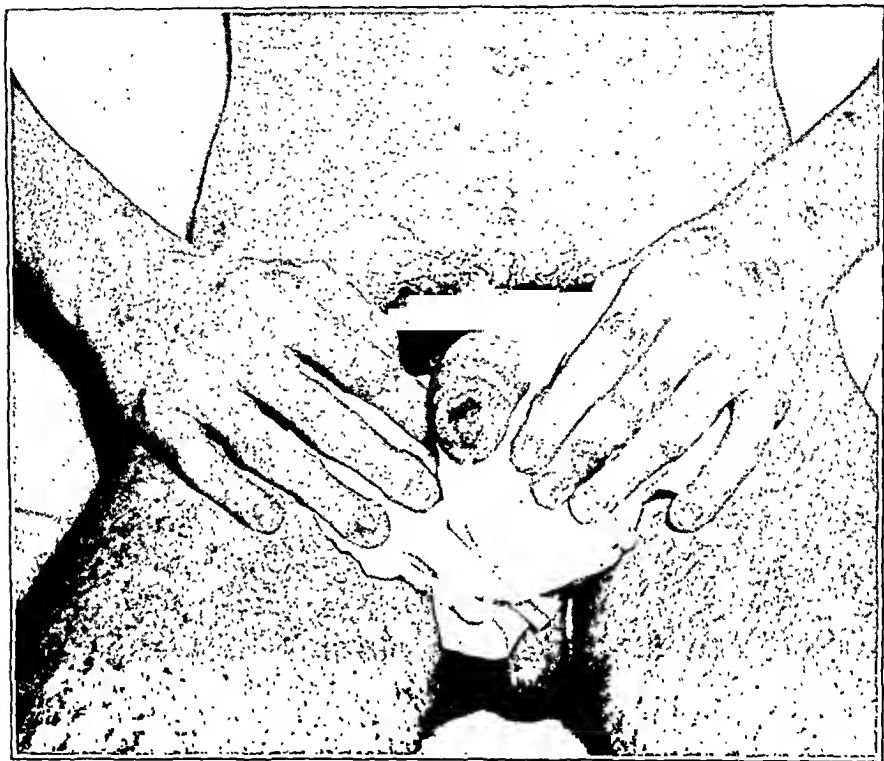


FIG. 3 E

FIG. 3.—Photographs taken 21 days after onset of initial symptoms of the Stevens-Johnson syndrome: A, Membranous exudate completely covered the tongue, and there was marked fissuring, excoriation and bleeding of lips. B, C, D and E, The bullæ of arms, forearms, lower extremities and trunk had receded considerably, and many showed central umbilication. Bullæ of the hands were still at their height. The superficial epithelium had desquamated from the scrotum and the glans penis.

Photographs were taken on the 26th hospital day (21 days after initial appearance of symptoms associated with Stevens-Johnson syndrome). By this time there had been considerable general and local improvement. Figure 3 shows clearly the cutaneous bullæ, many of which began to show central drying with umbilication. The stomatitis with membranous exudate completely covering the tongue is likewise clearly demonstrated.

Photographs were obtained again 1 week later (33rd day). Figure 4 demonstrates the further improvement which had occurred. Most of the cutaneous bullæ had dried completely. A few membranous plaques were still visible on the tongue.



A smear of the mouth failed to reveal Vincent's organisms. Examination of the oral membrane did not show the presence of fungi. Nose and throat cultures produced hemolytic streptococcus and hemolytic staphylococcus. The contents of the cutaneous vesicles repeatedly failed to reveal organisms on smear, and produced no growth on culture. No organisms were present



FIG. 4 B

FIG. 4.—Photographs taken 28 days after onset of symptoms of Stevens-Johnson syndrome. A, Grayish membranous plaques were still visible on the tongue. The lips were improved. B, the bullæ of the hands had dried. Reëpitheliazation of the glans had progressed.

on smear of the urethral meatus and a culture produced no growth. A culture of the ocular discharge yielded gram-positive diplococci. Blood cultures and urine examinations were negative. The blood N.P.N. was 30 and the blood sugar was 100. The blood Kahn was negative. Blood agglutination tests for typhoid, paratyphoid, tularemia and undulant fever were negative.

The Weil-Felix reaction and heterophile antibody tests were negative. Fifty-three intradermal skin tests for the common ingestants, contactants and inhalants were not contributory. Blood sulfadiazine concentrations ranged between 3.0 to 4.6 mg. per 100 gm. of the free drug.

**Discussion.** Case 1 presented the picture of severe membranous stomatitis, purulent conjunctivitis and involvement of the urethral meatus. No true exanthem was present, but this case clearly falls into this clinical syndrome. The acute course was short, lasting but 1 week, and the soldier made a complete recovery without complications. Oral sulfadiazine was administered in addition to local therapy to the mouth and eyes.

Case 2 was admitted to the hospital after Case 1 had completely recovered (17 days following admission of Case 1), and was kept under isolation for mumps. The 2 soldiers were students at different universities and at no time had they been in contact with each other. Six days after being admitted, Case 2 began to develop the typical characteristics of the Stevens-Johnson syndrome, *i. e.*, severe purulent conjunctivitis, vesicular and severe membranous stomatitis, associated with a vesicular and bullous cutaneous eruption. He became desperately ill and severely prostrated. Because of his precarious state both sulfadiazine and penicillin were administered. His course was extremely stormy throughout the 1st week and thereafter he improved slowly. The acute course lasted about 3 weeks. Although his vision remained unimpaired, a residual bilateral mild conjunctivitis and mild bilateral synechia remained. The effect of penicillin and sulfadiazine therapy cannot be evaluated in this single case. Certainly the response, if any, was neither dramatic nor prompt. Because of the history of having received a sulfonamide 1 year prior to admission and sulfadiazine 1 day before admission, a skin test to determine sulfonamide hypersensitivity was performed. The method described by Leftwich<sup>6</sup> was employed. Serum, obtained from a patient who had been receiving sulfadiazine for 5 days and which contained a free drug level of 7.7 mg. %, was used for the intradermal test. A negative result was obtained. Clinically the patient improved while receiving sulfadiazine therapeutically. Because of the negative intradermal test and improvement while under sulfadiazine therapy, the latter drug may be excluded from consideration as the causative agent.

Unfortunately these cases shed no further light upon the etiology of this bizarre syndrome. There was no evidence of sepsis or Vincent's infection in either case. The vesicles were sterile. Hemolytic streptococci, which were isolated from the throat cultures of both cases, may well have been secondary invaders. A strong impression exists that this syndrome is a systemic disease. It may well be that it is a virus infection with the clinical phenomena being toxic manifestations. Of interest is the fact that the symptoms in Case 2 were preceded by and associated with mumps (left parotid and right submaxillary). All doubt as to the diagnosis of mumps was dispelled when his roommate was admitted to the hospital, with mumps, 21 days following his admission date. In one previously reported case the symptoms

likewise started about 1 week subsequent to the onset of mumps.<sup>3</sup> It would be pure speculation at this point to hypothesize a relationship between this syndrome and mumps. However, a possibility arises that the virus of mumps in Case 2 was either the direct cause or indirectly predisposed the tissues to the entry of the etiologic virus. Further information must await investigation of future cases.

**Summary.** 1. Two cases of Stevens-Johnson syndrome of unknown etiology and characterized by an eruptive fever with membranous stomatitis, purulent conjunctivitis and severe constitutional reaction are reported.

2. These cases were encountered within a 2½ week interval with no history of contact with each other.

3. The first case was treated with sulfadiazine orally in addition to local therapy, and a complete recovery was made.

4. The second case was desperately ill and was treated with both sulfadiazine and penicillin. Following a protracted and extremely stormy course a complete recovery resulted, except for mild chronic residual conjunctivitis and bilateral ocular synechia.

5. The effect of either sulfonamide or penicillin therapy upon this syndrome cannot be properly evaluated from a review of these 2 cases.

6. A possible relationship of the etiologic agent to the virus of mumps is cited.

#### REFERENCES

1. AGELOFF, H.: Erythema Multiforme Bullosum With Involvement of Mucous Membranes of Eyes and Mouth (Stevens-Johnson's Disease): Report of a Case, *New England J. Med.*, 223, 217, 1940.

2. CHICK, F. E., and WITZBERGER, C. M.: Erythema Multiforme Exudativum Accompanying Oral Vincent's Infection, *Am. J. Dis. Child.*, 55, 573, 1938.

3. EDGAR, K. J., and SYVERTON, J. T.: Erythema Exudativum Multiforme With Ophthalmia and Stomatitis: Report of Two Cases in Children With Certain Observations on Histopathology and Animal Inoculation, *J. Pediat.*, 12, 151, 1938.

4. GINANDES, G. J.: Eruptive Fever With Stomatitis and Ophthalmia: Atypical Erythema Exudativum Multiforme (Stevens-Johnson's), *Am. J. Dis. Child.*, 49, 1148, 1935.

5. LEFTWICH, W. B.: An Intradermal Test for the Recognition of Hypersensitivity to the Sulfonamide Drugs. *Bull. Johns Hopkins Hosp.*, 74, 25, 1944.

6. MURPHY, R. C., JR.: An Eruptive Fever Involving the Mouth and Eyes (Stevens-Johnson's Disease): Report of a Case, *New England J. Med.*, 230, 69, 1944.

7. STEVENS, A. M., and JOHNSON, F. C.: New Eruptive Fever Associated With Stomatitis and Ophthalmia, *Am. J. Dis. Child.*, 24, 526, 1922.

---

#### EXPERIENCES WITH 2350 BLOOD TRANSFUSIONS AT AN ARMY GENERAL HOSPITAL IN INDIA

BY CAPT. CHARLES K. KIRBY, M.C., A.U.S.

20TH GENERAL HOSPITAL, APO 689, NEW YORK

DURING a 17-month period 2350 blood transfusions were given at this Army General Hospital in India, principally to combat troops. Approximately three-fourths of the transfusions were given to Chinese soldiers and one-fourth to Americans. Because of the lack of equipment commonly found in civilian blood banks, improvisation and modification of some techniques have been necessary. Experiences under these circumstances with transfusion reactions have emphasized

well established points concerning their cause and prevention. The use of universal donors for American patients has provided further evidence of interest in the current controversy regarding the advisability of this practice.

*Development of the Transfusion Service.* Among the first considerations when this hospital opened in April, 1943, was the establishment of a Blood Transfusion Service. Although an adequate supply of

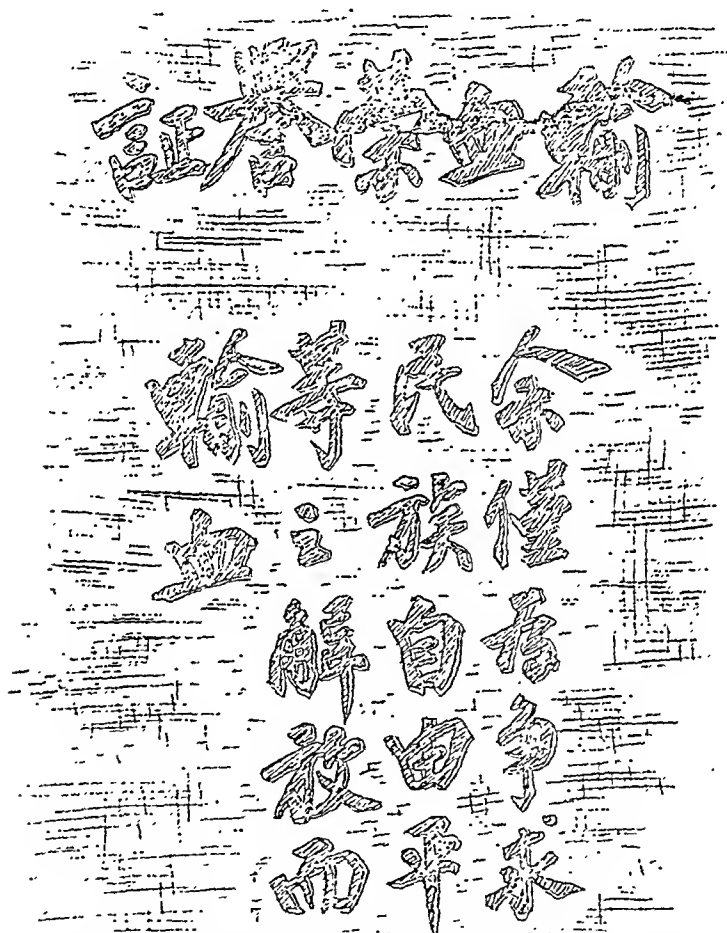


FIG. 1.—Certificate given to each Chinese blood donor. Translation: "I give my blood for liberty, equality, and the independence of China."

Red Cross plasma was available, the diseases endemic in this area and the tactical situation implied an early and steadily increasing need for whole blood. Typing sera were not available. They were obtained from medical officers and laboratory personnel of known types A and B and tested for potency. Blood transfusion apparatus was not available. Using commercial solution flasks with dental procaine carpules forced through holes in the rubber stoppers and tubing from plasma sets, a satisfactory semi-closed gravity system for

drawing blood was devised. Salvarsan burettes were used for administering blood. In May, 1943 the first transfusions were given and in June, 1943 the Chinese Blood Bank was opened.

An unusual and somewhat difficult problem has been the procurement of Chinese blood donors. The average, uneducated Chinese soldier, imbued since birth with the concept of personal thrift and unacquainted with the refinements of modern medicine, did not readily accept the idea of giving his blood to a fellow countryman unknown to him. As a result of much perseverance and tact on the part of our medical officers and the fullhearted coöperation of Lt. Col. An-Chuen Ma of the Chinese Army, this resistance is gradually being overcome. For many months a mobile blood procurement team visited Chinese units along the Ledo Road but at present Chinese donors are reporting to this hospital twice a week. Shown in Figure 1 is the certificate given to each Chinese blood donor.

For the first few months blood for American patients was obtained from members of the Medical Detachment by ward officers. In February, 1944 the increasing demand necessitated the establishment of a separate American Blood Bank, with donors reporting from many units in this area. Beginning with 17 transfusions during June, 1943 the number of transfusions each month steadily increased, reaching a maximum of 355 during July, 1944. From June, 1943 through October, 1944 the 17-month period covered by this report, a total of 2350 blood transfusions were given, 1732 to Chinese and 618 to American patients.

**Methods and Techniques.** Typing sera were obtained from suitable A and B donors and tested for potency by the method of Coca. Following inactivation they have been stored under sterile conditions.

For blood typing the open slide method of Vincent has been used. With typing sera of adequate strength it has proved to be very reliable. Not infrequently the blood type recorded on the donors' "dog tag" has been found to be incorrect. For compatibility tests the open slide method was used for several months. In February, 1944 this was abandoned in favor of the centrifuged test tube method of Levine because of its greater speed and more clear cut reactions. In the absence of macroscopic agglutination microscopic checks have been made routinely. Rh antiserum was not available for determining the presence or absence of the Rh agglutinin.

Cold agglutinins have been sought for when indicated but no attempt has been made to identify other minor hemagglutinins or the sub-groups.

Only blood less than 7 days old with a negative Kahn and negative malaria smear has been used for transfusion. Despite the high incidence of malaria in this area, American donors with a negative malaria history have been available most of the time. In a few instances donors who had a single malaria attack more than 9 months previously have been used. No clinical or laboratory evidence of malaria transmission has resulted from these transfusions. In Chinese, because of the very high incidence of malaria and the difficulty in obtaining donors, the malaria history has been ignored, even though an attack occurred less than 1 month prior to the blood donation. Despite a negative blood smear, it is not unlikely that malaria was transmitted by some of these transfusions. Unfortunately the press of work prevented study of this problem. Malaria transmission would be difficult to establish with certainty in the Chinese because of the frequency of chronic recurrent malaria among the recipients and the possibility of a primary infection occurring while in the hospital.



In Americans the type O so-called "universal donor" was used for most of the transfusions. Intragroup transfusions were not feasible without an excessive waste of blood because of the unpredictability of the amount of blood and the blood types needed from day to day and week to week. Agglutinin titers of type O blood have not been determined because of the lack of sufficient laboratory personnel.

In Chinese patients intragroup transfusions were given almost exclusively. Because of the frequency of transfusions and the relatively rapid replacement of blood, the disproportion between the types of donors and recipients has not at any time been great.

The relative frequency of type B blood in the Chinese was striking. Table 1 shows the frequency in per cent of blood types of 1000 consecutive Chinese donors as compared with figures for the American white population taken from a standard textbook.<sup>9</sup>

TABLE 1.—FREQUENCY (%) OF BLOOD TYPES OF CHINESE AND AMERICANS

International type	Chinese	Americans
O . . . . .	39	44
A . . . . .	28	40
B . . . . .	26	10
AB . . . . .	8	6

All donors have been tapped with the improvised semi-closed gravity apparatus mentioned above. Only 300 cc. of blood were taken from Chinese donors because of their smaller stature and correspondingly smaller blood volume. Sodium citrate (3.5%) prepared in our central dressing room was used as an anticoagulant, 50 cc. for 300 cc. of Chinese blood and 70 cc. for 500 cc. of American blood. Transfusions were given by the open method, pouring blood from the donor bottle through a gauze filter into a salvarsan burette. Commercial donor and recipient equipment (Baxter) has recently been received and it is planned to replace the present equipment with it.

*Indications.* The majority of the transfusions were given for shock and anemia due to blood loss in battle casualties. Large amounts of blood for individual patients have frequently been necessary, particularly in wounds of the cranial, thoracic, and abdominal cavities. During later months an increasing number of transfusions were given for sepsis, acute and chronic, with and without marked anemia. Less common indications were thermal burns, malaria with marked hemolysis, scrub typhus, and operative procedures associated with significant blood loss (*e. g.*, bone grafts).

Recently the effect of immuno-transfusion in scrub typhus was investigated on a small scale. Whole blood and pooled plasma from convalescent cases were given to patients in various stages of the disease, without apparent beneficial effect.

In this hospital there has been a marked preference for the use of whole blood over plasma in the treatment of battle casualties, both in the early stages immediately after wounding and during the later stages of definitive treatment. In contrast to the 2350 whole blood transfusions given during this 17-month period, there were only 934 transfusions of liquid and dried plasma. Although in some instances plasma has been given to deeply shocked patients while blood was being cross-matched, the use of plasma at any stage in the treatment of

battle casualties has been very infrequent. Most of the plasma transfusions have been given for severe thermal burns during the acute stage of plasma loss. In a few cases plasma has been used to correct hypoproteinemia not associated with significant anemia.

*Chinese Plasma Bank.* Because no source of plasma was available for the Chinese, a Chinese Plasma Bank was established in conjunction with the Chinese Blood Bank. Plasma from blood unsuitable for transfusion was pooled with suitable distribution of the blood types, creating a reserve of liquid plasma which has more than satisfied the requirements of this hospital. From June, 1943 through October, 1944 271 bottles (97,850 cc.) of this plasma have been used. At present there is a reserve on hand of 204 bottles (71,400 cc.), much of which will be sent to units in more forward areas. Pyrogenic reactions accompanying transfusion of this plasma have been frequent, averaging about 25%. There have been no hemolytic reactions.

*Reactions to Blood Transfusions.* Transfusion reactions have been divided into 3 groups: (1) hemolytic; (2) proteolytic, including allergic manifestations of all types and degrees of severity; and (3) pyrogenic, including chills and fever as well as fever alone. Of the 2350 transfusions, 482 have been complicated by reactions, an overall incidence of 20.51%. No reaction has been fatal. The number of reactions of each type and their relative percentages are shown in Table 2.

TABLE 2.—ANALYSIS OF REACTIONS IN 2350 BLOOD TRANSFUSIONS

Type of reaction	No.	%
Hemolytic . . . . .	2	0.085
Proteolytic . . . . .	79	3.361
Pyrogenic . . . . .	401	17.064
Total . . . . .	482	20.510

The two hemolytic reactions occurred during July, 1943. Both were in Chinese patients and were due to errors in typing. An incidence of 0.085% of hemolytic reactions compares favorably with figures reported in transfusion series of comparable size,<sup>1,10</sup> and with 0.18% in a series of over 40,000 transfusions collected by Kilduffe and DeBakcy.<sup>4</sup> The laboratory technicians responsible for this record deserve much credit.

An incidence of 3.361% of proteolytic reactions is somewhat higher than has been reported in the United States.<sup>3,4</sup> It is thought that this may be due to a greater frequency of allergic manifestations in this area. A similar situation was found in skin disease. Although there have been a few instances of moderately severe angioneurotic edema, most of these reactions have consisted of mild urticaria. Anaphylactic shock has not occurred.

Because of the lack of adequate equipment and facilities for cleaning transfusion apparatus, pyrogenic reactions were relatively frequent for many months. Sodium dichromate and sulfuric acid were not available for cleaning glassware and there were no facilities for washing glassware or rubber tubing under pressure. Rubber tubing was of

necessity used far beyond the usual and desirable time for discard. The chief factor causing many of these reactions was the use of narrow-neck plasma bottles in Chinese donor sets. Removing pyrogens from these bottles, whose necks measure 6 mm. in diameter, was found to be extraordinarily difficult and uncertain without special equipment.

In August, 1944 adequate materials for cleaning glassware were obtained and a device for washing rubber tubing under pressure was installed. At the same time it was possible to replace the narrow-neck plasma bottles in Chinese donor sets with wide-neck commercial solution flasks. The decrease in pyrogenic reactions was dramatic. In contrast to an incidence of 22.71% of chills and fever during July and August, 1944 only 4.5% of transfusions were complicated by these reactions during September and October, 1944. With further improvements in cleaning facilities and additional refinements in the cleaning technique it is believed that these reactions could be virtually eliminated. The cleaning procedure used was similar to that which enabled Lewisohn and Rosenthal<sup>6</sup> to reduce pyrogenic reactions from 12% to 1%.

Three of the possible factors investigated in connection with the pyrogenic reactions proved to be of little, if any, significance. These were: (1) delayed refrigeration, (2) agitation of blood during transportation by truck, and (3) the open method of giving transfusions. The first two factors were eliminated by discontinuing the mobile blood procurement team and having the donors report to the hospital where the blood was immediately refrigerated without agitation. This was done at a time when reactions were frequent among Chinese patients, but the incidence of reactions was not reduced, in fact, it was higher following the change.

The open method was still in use after the incidence of reactions had been satisfactorily reduced by improvement in the cleaning technique, and it, therefore, seems reasonable to conclude that it had played little, if any, rôle in causing the reactions.

**Comment.** The blood transfusions herein reported have occupied a position of great importance among the therapeutic measures employed in this hospital. As has been found in other theaters of operations, whole blood is essential for the successful treatment of many battle casualties.

Although the danger of hemolytic reactions resulting from the iso-immunization of Rh negative individuals by repeated transfusions of Rh positive blood is well recognized, no such reaction has occurred in this series. In this regard the opinion of Simmons and Gentzkow<sup>8</sup> "that such reactions will not constitute a serious military problem" is of interest. In the Chinese, who are virtually 100% Rh positive,<sup>5</sup> this factor may probably be safely ignored. Rh antiserum (dried) has recently been received and its use in protecting American patients receiving multiple transfusions is planned.

The use of universal donors, condemned by many writers because of the danger of hemolysis resulting from the transfusion of incompatible isoagglutinins, has resulted in no hemolytic reactions in this series of transfusions in American patients. This corresponds with the experience of Harrison<sup>2</sup> in World War I and supports the opinion of Rosenthal and Vogel<sup>7</sup> that "one should not hesitate to recommend this practice for our own troops." Intragroup transfusions are, of course, to be preferred when possible.

Although not serious in any instance, the frequency of pyrogenic reactions for many months was troublesome, particularly in sick patients. Our experience with these reactions emphasizes the importance of meticulous cleansing of all blood transfusion paraphernalia.

**Summary.** 1. An analysis of 2350 blood transfusions given to Chinese and American troops at an Army General Hospital in India has been made.

2. Whole blood was used in larger quantities than liquid and dried human plasma in treating battle casualties.

3. Type B blood was found to be somewhat commoner in Chinese than in Americans.

4. Proteolytic reactions occurred more frequently than has been reported in the United States.

5. Use of the universal donor for American patients and multiple transfusions given without regard for the Rh factor resulted in no hemolytic reactions.

6. A high incidence of pyrogenic reactions due to inadequate facilities for cleaning transfusion apparatus was markedly reduced by institution of improved methods of removing pyrogens.

#### REFERENCES

1. DE GOWIN, E. L.: Grave Sequelæ of Blood Transfusions: A Clinical Study of 13 Cases Occurring in 3500 Blood Transfusions, *Ann. Int. Med.*, **11**, 1777, 1938.
2. HARRISON, B. I.: Blood Transfusion at the Front Area, *J. Am. Med. Assn.*, **71**, 1403, 1918.
3. Hoxworth, P., and SKINNER, C.: Improvement in Blood Transfusion Service: III. Results of 3077 Transfusions of Banked Blood: A Statistical Analysis, *Arch. Surg.*, **42**, 498, 1941.
4. KILDUFFE, R. A., and DE BAKEY, M.: The Blood Bank and the Technique and Therapeutics of Transfusions, St. Louis, C. V. Mosby, 1942.
5. LEVINE, P., and WONG, H.: The Incidence of the Rh Factor and Erythroblastosis Fetalis in Chinese, *Am. J. Obst. and Gynec.*, **14**, 832, 1943.
6. LEWISOHN, R., and ROSENTHAL, N.: Prevention of Chills Following Transfusion of Citrated Blood, *J. Am. Med. Assn.*, **100**, 466, 1933.
7. ROSENTHAL, M. D., and VOGEL, P.: Observations on Blood Transfusions From Universal Donors, in Mudd and Thalheimers' Blood Substitutes and Blood Transfusion, Springfield, Ill., Thomas, 1942.
8. SIMMONS, J. S., and GENTZKOW, C. J.: Laboratory Methods of the United States Army, 5th ed., Phila., Lea & Febiger, 1944.
9. STITT, E. R., CLOUGH, P. W., and CLOUGH, M. C.: Practical Bacteriology, Hematology and Parasitology, 9th ed., Phila., Blakiston, 1938.
10. TURNER, O. E.: Investigation of Transfusion Reactions, *Penna. Med. J.*, **47**, 1071, 1944.

# A SIMPLE TECHNIQUE OF STERNAL MARROW BIOPSY FOR SPREADS AND SECTIONS

By ELIZABETH MERTENS, M.D.

ASSISTANT INSTRUCTOR IN PATHOLOGY

PHILADELPHIA, PENNSYLVANIA.

(From the Division of Pathology, Philadelphia General Hospital, and the Department of Pathology, University of Pennsylvania Medical School)

There are two methods that are usually employed to obtain bone marrow from the sternum: the aspiration method and the trephine method. The aspiration method has the advantage that it can be performed with ease. It is a ward procedure which offers little discomfort to the patient and which can be repeated at frequent intervals. The disadvantage of this method is that while the films made from aspirated marrow are excellent for the study of cellular details, they do not permit an accurate estimation of the quantitative relationships of the cells nor do they allow a histopathologic study of the marrow structure.

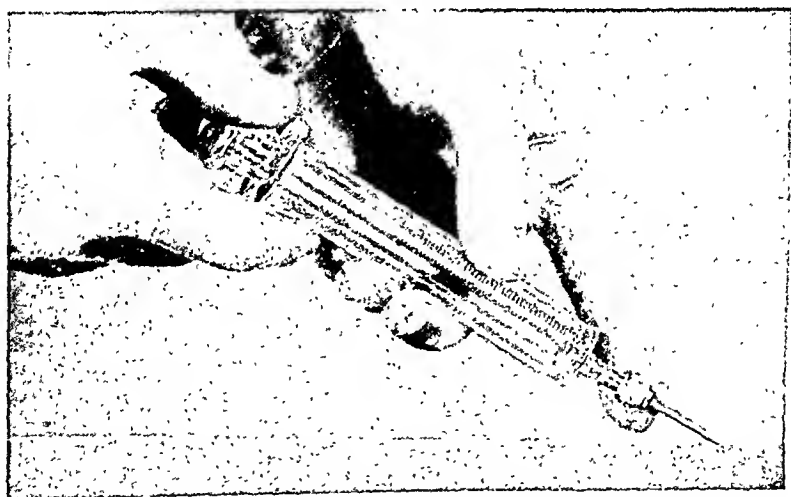


FIG. 1.—Position of syringe during aspiration of bone marrow.

The trephine method, on the other hand, has the advantage that it offers sufficient marrow tissue for a satisfactory histopathologic study. The disadvantage of this method is that it is a surgical procedure. It requires special equipment, necessitates an incision of the skin, and cannot be repeated at frequent intervals.

During the last year we have devised and used routinely a simple technique which not only combines most of the advantages of the aspiration and the trephine methods, but eliminates their disadvantages. Our technique resembles the usual aspiration technique in that we puncture the sternum and aspirate marrow tissue and blood. It differs from the usual aspiration method in that the blood is allowed

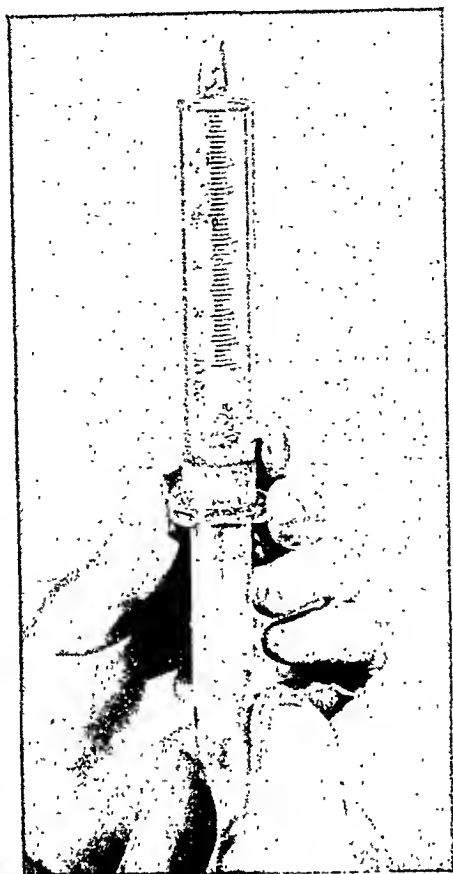


FIG. 2.—Position of syringe in which the specimen is allowed to clot.

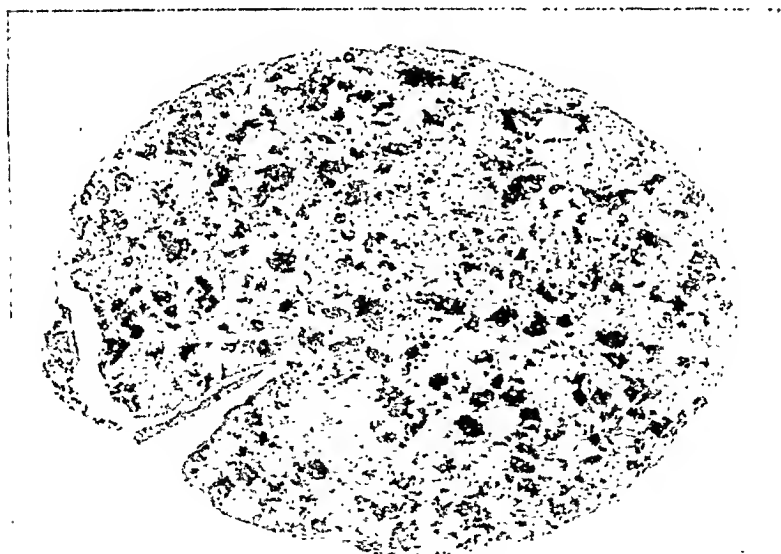


FIG. 3.—Complete section through the disk-shaped clot, from a patient with pernicious anemia. Note the numerous dark particles of marrow contained in the clot. Azure II Eosin,  $\times 8$ .

to clot so that the tissue particles form a disk which without decalcification can be cut and stained as readily as any other tissue.

**Technique.** The site of puncture is a point determined by the mid-line of the sternum and a line through the level of the upper margin of the third costal cartilage. The skin over this and the surrounding area is prepared by shaving, cleaning and applying an antiseptic solution. The skin, subcutaneous tissue, and periosteum are then infiltrated with 1% novocaine. When anesthesia is complete, the needle, a 15 gauge Osgood sternal puncture needle, is inserted with the stylet in place, until the anterior lamella of the sternum is penetrated. When the tip of the needle has entered the marrow cavity the stylet is removed and with very gentle pressure and a slight rotatory motion the needle is forced into the marrow cavity at an angle of 30 to 40 degrees for a distance of not more than 7 mm. in an adult, or until the tip first meets the greatly increased resistance of the posterior lamella. A dry 10 cc. syringe is then attached and sternal marrow and blood are aspirated until the specimen reaches a depth of 2 or 3 mm. in the syringe. It should not be neglected to remove the stylet before the needle is forced through the marrow cavity so that its lumen gathers marrow tissue in passing. It is important that the capillary of the syringe tip should have a bore equal in diameter to that of the needle so that the marrow particles will meet no obstruction in passing from the lumen of the needle into the syringe.

As soon as the material has been obtained, the syringe is detached and the stylet returned to the needle in the sternum. The syringe is changed immediately from the horizontal position (Fig. 1) to a vertical one (Fig. 2) and the plunger is withdrawn until its distal end is approximately 1 cm. above the mouth of the syringe. The specimen is allowed to clot in this position. When it has clotted well, the plunger is removed completely and the specimen which adheres lightly to its distal end is dropped into freshly prepared Zenker's formal solution for fixation.

Inspection of the clotted specimen shows small gray or yellow particles which are either concentrated on one or the other surface of the clot or evenly dispersed within it depending upon the relative specific gravities of the marrow particles and the marrow blood. After fixation, the specimen is washed, dehydrated, cleared and embedded in paraffin in such a way that the greatest number of marrow particles are exposed for section. The sections are made and stained with Azure II Eosin by routine methods.

If films are desired, the needle is withdrawn until its tip is at the level of the anterior lamella, the stylet is then removed and the needle is reinserted into the marrow cavity as before, but in a slightly different direction. A second syringe is attached and a second specimen aspirated. When the syringe has been detached the stylet is reinserted and the sternal needle removed as a collodion dressing is applied.

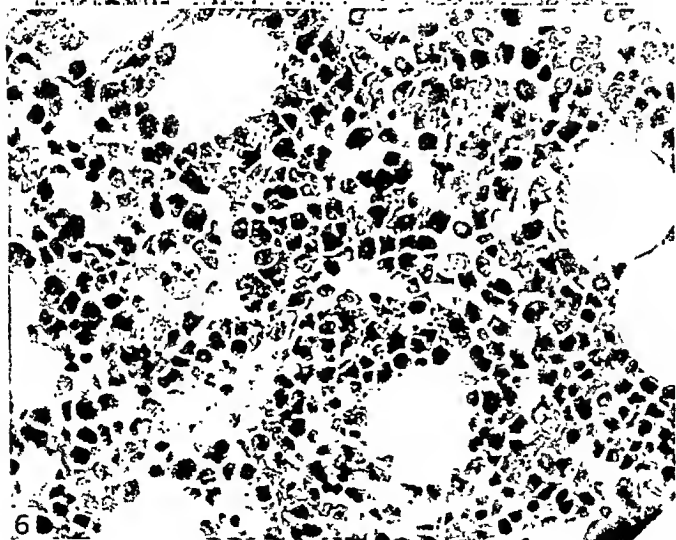
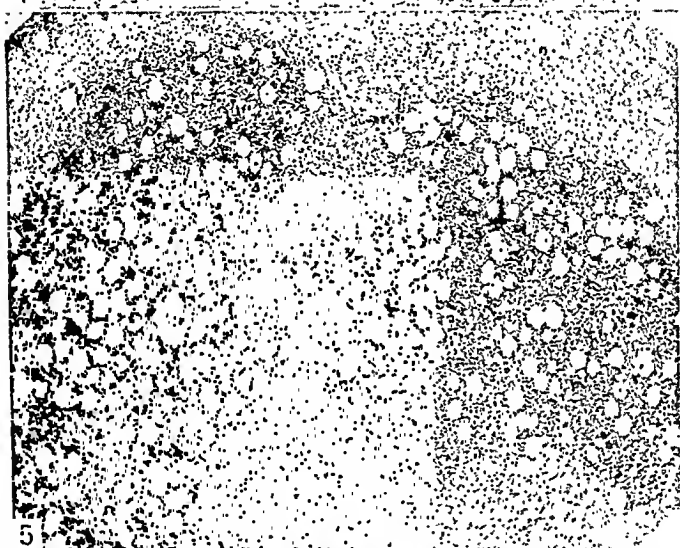
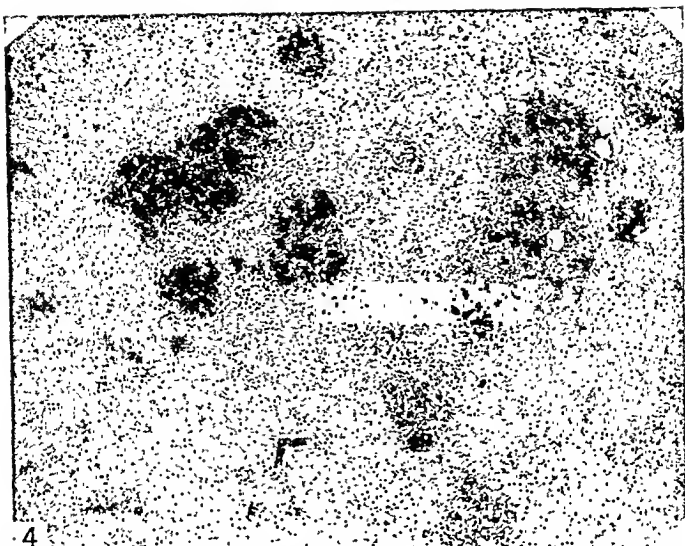
**Results.** Some results obtained with our method are presented in Figures 3 to 6. Figure 3 shows a complete section through the disk-shaped clot; the particles of marrow appear dark in the illustration. Figure 4 shows comparatively few small particles of marrow, while Figure 5 represents a biopsy containing many large pieces. Figure 6, finally, represents a higher magnification of Figure 5; the latter shows

#### LEGENDS FOR FIGS. 4, 5 AND 6.

FIG. 4.—Section through clot containing comparatively few small marrow particles' from patient suffering from post-hemorrhagic anemia. Azure II Eosin,  $\times 80$ .

FIG. 5.—Section through clot containing many large marrow particles, from patient suffering from subacute bacterial endocarditis. Azure II Eosin,  $\times 80$ .

FIG. 6.—Same as Figure 5.  $\times 640$ .



FIGS. 4, 5 and 6.



an inflammatory response in a patient with subacute bacterial endocarditis.

**Summary.** A simple technique of sternal marrow biopsy is described which combines the advantages of the aspiration and the trephine methods. Figures 3 to 6 show representative results obtained with this method.

## THE EFFECT OF VITAMIN K<sub>1</sub> OXIDE UPON THE ANTI-COAGULANT PROPERTIES OF DICUMAROL\*

BY CHARLES S. DAVIDSON, M.D., C.M.

JOHN H. FREED, M.D.

AND

HARRIET MACDONALD, B.S.

BOSTON, MASSACHUSETTS.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services [Harvard], Boston City Hospital, and the Department of Medicine, Harvard Medical School)

DICUMAROL [3-3'-methylenebis (4-hydroxycoumarin)] has been used as an anticoagulant in disease conditions in which diminished coagulability of the blood is desired.<sup>1,2,3,4</sup> The clinical usefulness of dicumarol is limited by the slow and difficult reversibility of the impaired blood coagulability as evidenced by a prolonged coagulation time.<sup>5</sup> The action of dicumarol may be contrasted with that of heparin after the injection of which the prolonged blood coagulation time may be brought at once to normal by the administration of suitable amounts of protamine.<sup>6</sup>

Overman, Stahmann and Link<sup>7</sup> were able to show an antagonistic action of the vitamin K-like substance 2-methyl-1, 4-naphthoquinone to dicumarol administered to rabbits. Shapiro<sup>8</sup> and Davidson and MacDonald<sup>9</sup> confirmed this in man, the latter authors using the oxide of vitamin K<sub>1</sub>.

The amount of dicumarol used by these investigators was below that required to prolong the blood coagulation time significantly, although the prothrombin time was prolonged in all instances. Lucia and Aggeler<sup>10</sup> demonstrated the effectiveness of vitamin K<sub>1</sub> oxide in returning the coagulation time to normal in 1 patient given dicumarol in sufficient amounts to produce prolongation of the coagulation time. The present report is concerned with the effect of the administration of vitamin K<sub>1</sub> oxide upon the *blood coagulation time* of patients who had been given dicumarol in amounts sufficiently large and for a sufficiently long time to prolong the blood coagulation significantly above normal.

**Methods.** The venous blood coagulation time was measured in glass tubes at 37° C. by a modification<sup>11</sup> of the method of Lee and White<sup>12</sup> (normal values 6 to 12 minutes). The prothrombin time was measured by a modification<sup>13</sup> of Quick's method.<sup>14</sup> The thromboplastin used in this test clotted normal plasma in from 20 to 25 seconds.

\* The expenses of this investigation were defrayed in part by a grant given "In recognition of Dr. Francis W. Peabody's Services to the Foundation," by the Ella Sachs Plotz Foundation.

Dicumarol\* was administered orally in gelatin capsules. Vitamin K<sub>1</sub> oxide was given intravenously in an alcohol-water emulsion prepared by a modification<sup>9</sup> of the method of Seligman.<sup>15</sup>

**Results.** Eleven patients were given dicumarol orally in varying amounts. Four patients had evidence of thrombophlebitis, 1 with obstructive jaundice as well. The remaining 7 patients were convalescing from acute illnesses. Their ages were from 43 to 75 years.

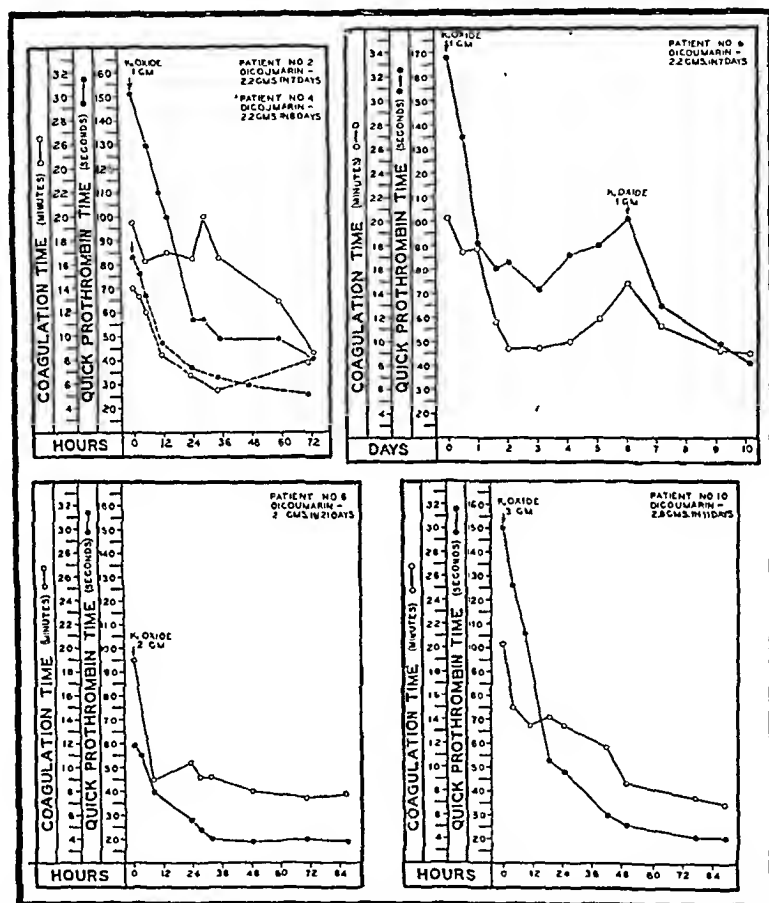


FIG. 1.—Antagonistic effect of vitamin K<sub>1</sub> oxide upon the anticoagulant effect of dicumarol in 5 patients.

From 3 to 21 days after the administration of from 1 to 3.6 gm. of dicumarol, the blood coagulation time, which had been within normal limits, became prolonged (over 12 minutes) in all 11 patients. The initial dose of dicumarol was from 0.5 to 1 gm., followed usually by a daily dose of 0.2 gm. One patient, No. 8, was given 0.8 gm. of dicumarol initially and thereafter the dosage was regulated to maintain his prothrombin time between 30 and 60 seconds. One patient, No. 11, after 8 days of therapy had a sudden and severe gastric hemorrhage and died before remedial therapeutic measures could be instituted. His coagulation time, the day of his death, was elevated to 18½ minutes.

\* Kindly furnished by the Abbott Laboratories, North Chicago, Ill.

To the remaining 10 patients from 0.5 to 3 gm. of vitamin K<sub>1</sub> oxide was given intravenously in from 1 to 2½ hours. The blood coagulation time returned to normal in from 3½ to 36 hours in each of these patients (Fig. 1).

Of the 10 patients given vitamin K<sub>1</sub> oxide, 3 (Nos. 1, 2 and 5) were given 0.2 gm. of dicumarol without interruption for 6, 8 and 12 days thereafter. The coagulation time remained normal in the patient to whom administration of the drug was continued for 2 days. The patient to whom administration was continued for 6 days (No. 5) had

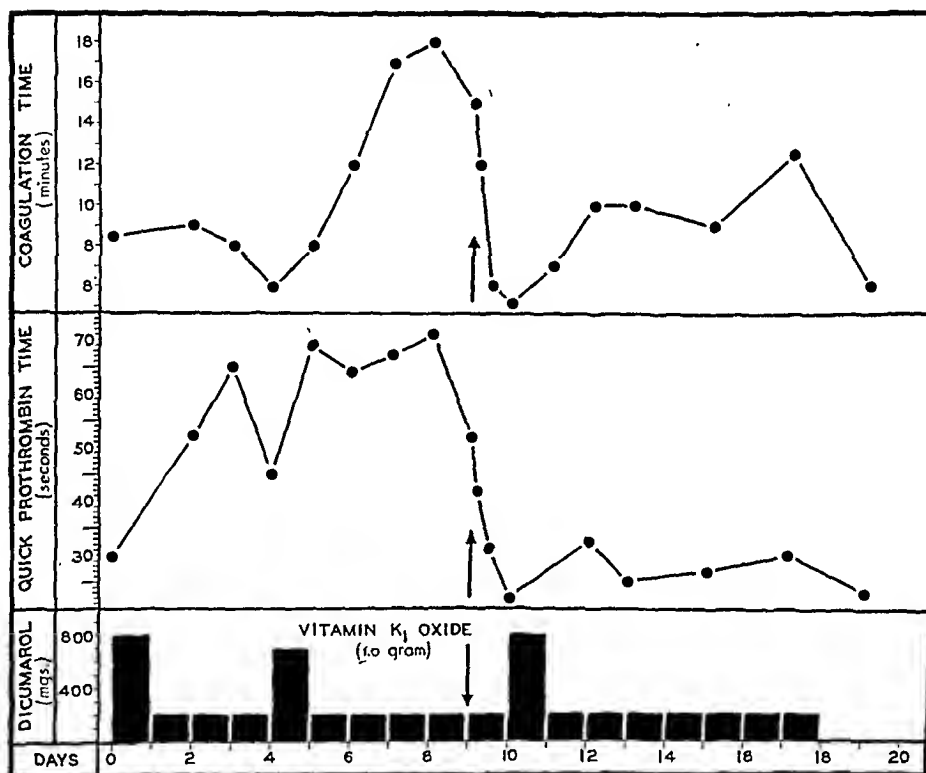


FIG. 2.—Antagonistic effect of vitamin K<sub>1</sub> oxide upon the anticoagulant effect of dicumarol in spite of continued administration of dicumarol.

a normal coagulation time for 5 days, but on the 6th day his coagulation time rose to 16 minutes. Patient 1 was given 0.2 gm. dicumarol daily for 8 days (Fig. 2) and was then given 1 gm. of vitamin K<sub>1</sub> oxide. On the next day he was given an additional 0.8 gm. of dicumarol, but in spite of this his coagulation time remained normal for the succeeding 8 days.

**Discussion.** The action of large amounts of vitamin K<sub>1</sub> oxide in reversing the hypoprothrombinemia induced by dicumarol is equally effective in reversing the prolonged coagulation time in the 10 patients reported here. This effect is seen even if the administration of dicu-

marol is continued after the vitamin K<sub>1</sub> oxide has been given. However, after the administration of vitamin K<sub>1</sub> oxide, normal blood coagulation times did not occur for from 3½ to 36 hours. Thus the control of the abnormal blood coagulability is not rapid enough to prevent excessive loss of blood if brisk hemorrhage were to ensue. This is clearly illustrated in Patient 11 who died of hemorrhage. In his case had heparin been used instead of dicumarol it might have been possible by the use of protamine to bring his coagulation time to normal and stop the bleeding. Therefore, it seems evident that if a prolonged blood coagulation time is desired and dicumarol is used, control of the coagulation time must be sacrificed to a dangerous degree.

Clinical evidence is accumulating which suggests that at least to prevent phlebothrombosis postoperatively, doses of dicumarol small enough to prolong the prothrombin time, but not the coagulation time, may be effective.<sup>16,17</sup> If these reports are substantiated it may be that such a use may be an important contribution to therapeutics. Nevertheless, when reduced blood coagulability of a greater degree is desired as after vascular surgery, the lack of control using dicumarol, even with vitamin K, makes it an unsafe drug for use at present.

**Summary.** 1. The prolonged blood coagulation time following the ingestion of dicumarol was returned to normal in from 3½ to 36 hours by the intravenous administration of large amounts of vitamin K<sub>1</sub> oxide in 10 patients.

2. This effect was evident in spite of the continued administration of dicumarol.

3. Following the administration of dicumarol 1 patient died of severe bleeding before control could be instituted.

4. The use of dicumarol in conditions requiring prolongation of the blood coagulation time is at present still dangerous because of lack of control.

#### REFERENCES

1. MEYER, O. O., BINGHAM, J. B., and AXELROD, V. H.: *AM. J. MED. SCI.*, 204, 11, 1942.
2. BUTSCH, W. L., and STEWART, J. D.: *Arch. Surg.*, 45, 551, 1942.
3. BRAMBEL, C. E., and LOKER, F. F.: *Arch. Surg.*, 48, 1, 1944.
4. BARKER, N. W., ALLEN, E. V., and WAUGH, J. M.: *Proc. Staff Mect.*, Mayo Clin., 16, 388, 1941.
5. DAVIDSON, C. S., and MACDONALD, H.: *AM. J. MED. SCI.*, 205, 24, 1943.
6. CHARGAFF, E., and OLSON, K. B.: *J. Biol. Chem.*, 125, 671, 1938.
7. OVERMAN, R. S., STAHMANN, M. A., and LINK, K. P.: *J. Biol. Chem.*, 145, 155, 1942.
8. SHAPIRO, S., REDISH, M. H., and CAMPBELL, H. A.: *Proc. Soc. Exp. Biol. and Med.*, 52, 12, 1943.
9. DAVIDSON, C. S., and MACDONALD, H.: *New England J. Med.*, 229, 353, 1943.
10. LUGIA, S. P., and AGGELER, P. M.: *Proc. Soc. Exp. Biol. and Med.*, 56, 36, 1944.
11. POHLE, F. J., and TAYLOR, F. H. L.: *J. Clin. Invest.*, 16, 741, 1937.
12. LEE, R. I., and WHITE, P. D.: *AM. J. MED. SCI.*, 145, 495, 1913.
13. SOUTER, A. W., and KARK, R.: *AM. J. MED. SCI.*, 200, 603, 1940.
14. QUICK, A. J., STANLEY-BROWN, M., and BANGROFT, F. W.: *AM. J. MED. SCI.*, 190, 501, 1935.
15. SELIGMAN, A. M., HURWITZ, A., FRANK, H. A., and DAVIS, W. A.: *Surg., Gynec. and Obst.*, 73, 686, 1941.
16. LAM, C.: *J. Michigan State Med. Soc.*, 42, 968, 1943.
17. BARKER, N. W.: *Minnesota Med.*, 27, 102, 1944.

## FINAL NOTE ON A REPORTED CASE OF ERYTHREMIA, GOUT AND SUBLEUKEMIC MYELOSIS

BY GEORGE H. REIFENSTEIN, M.D.

ASSOCIATE PROFESSOR OF PATHOLOGY

SYRACUSE, NEW YORK.

(From the Department of Pathology, Syracuse University College of Medicine)

IN 1939 I reported in this journal a case of erythremia, gout, anemia and the blood smear and bone marrow characteristics of subleukemic myelosis in a female patient observed during a 5-year period.<sup>4</sup> The statement was made that "the subsequent course may determine the proper designation." In view of the fact that the further clinical course and autopsy findings of this patient are available, this subsequent report is presented.\*

*Subsequent Clinical Observations.* After discharge from the hospital in April, 1938, the patient continued to show severe anemia, splenomegaly, considerable dyspnea, some pain in the lower sternum and slowly lost weight. In November, 1939 she was admitted to a hospital because of recurrence of a lesion on her nose, and persistent splenomegaly and anemia. Examination showed slight wasting, marked pallor, a small basal-cell carcinoma of the nasal tip, no palpable lymph nodes and a non-transmitted systolic murmur at the cardiac apex. The lower border of the spleen reached below the iliac crest, the right border extended at least 4.5 cm. beyond the umbilicus, and the spleen was described as "hard and rocky" and "projecting anteriorly in a manner not unlike pregnancy." There were many varicosities in the lower extremities and tophi palpable in the dorsum of the distal phalangeal joint of each first phalanx of the feet. Examination otherwise was not remarkable. At that time the erythrocytes were 2,800,000 per e.mm., hemoglobin 43%, and the leukocytes 7100 (45% neutrophils, 27% band cells, 1% eosinophils, 7% small lymphocytes, 1% "young monocytes," 8% neutrophilic myelocytes, 5% metamyelocytes, 2% "young cells," and 4% "stem cells"). Other studies showed ieteric index 12.5, blood uric acid 12 mg., N.P.N. 27 mg. per 100 cc., and metabolic rate + 68.

The patient received blood transfusions but gradually became weaker. A splenic puncture showed what was described as "myeloid metaplasia." A sternal biopsy showed "a hyperactive marrow with megakaryocytes." She received 200 r high voltage Roentgen ray in divided doses directed to the anterior splenic area. In February, 1940 the erythrocytes were 2,460,000 per e.mm., hemoglobin 48%, and leukocytes 3800 per e.mm. There was no significant change in splenomegaly. The patient was discharged and died in March, 1940, approximately 8 years after she first noted a left abdominal mass.

*AUTOPSY* (significant features of gross findings). External examination showed marked pallor and slight ieterus. There was no palpable lymphadenopathy. The subcutaneous tissues of the trunk were wasted and edematous. The *peritoneal cavity* contained approximately 200 cc. of clear straw-colored fluid. The right *pleural cavity* contained approximately 1200 cc. of clear straw-colored fluid, the left *pleural cavity* approximately 1000 cc. and the *pericardial cavity* approximately 50 cc. of similar fluid. The *heart* weighed 300 gm. and was greatly dilated. The myocardium was slightly paler and softer than usual. The *liver* (1800 gm.) was smooth and brownish and had

\* I am indebted to Dr. S. C. Dalrymple, Newton, Mass., and Drs. Shields Warren and R. W. Rawson, Boston, whose kind cooperation has made available the subsequent clinical observations, gross autopsy findings and tissue for microscopic study.

an appearance suggestive of considerable hemosiderin deposition. Its edge was 4 fingerbreadths below the costal margin; the left lobe was 5 fingerbreadths below the ensiform cartilage, extending well into the left quadrant. The *spleen* (1290 gm.) was greatly enlarged, the anterior pole lying almost to the midline at the level of the umbilicus. Its capsule was smooth except for two small areas of infarction on its upper border. These areas measured approximately 2 cm. in diameter and were deep red and reddish gray in color. The remainder of the spleen was firm and reddish with innumerable irregular deeper red patches throughout. The left *kidney* weighed 100 gm., the right 120 gm. Cut surfaces appeared pale with slight cortical narrowing. The calices and pelves showed no dilation and contained brownish granular material. In the left kidney pelvis was a lima bean-sized stone of similar material measuring 2 cm. in length. Chemically it showed a nucleus of uric acid with an outside coating of uric acid and ammonium urate. The *ureters* were edematous but not dilated. The *mesentery* contained a few small scattered pea- and bean-sized nodes which were soft, white and grossly not remarkable. The portal, superior mesenteric and splenic *veins* were without evident lesion. Rib, vertebral and femoral *marrow* was deep red; that in the femur seemed gritty. The lungs, pancreas, adrenals, bladder, uterus, tubes, ovaries, thyroid, esophagus, stomach, small intestine and large intestine were without evident lesion except for slight edema of the wall of the gastro-intestinal tract.

**MICROSCOPIC FINDINGS.** Sections of *spleen* showed an increased amount of pulp diffusely infiltrated with large numbers of early leukocytes of the myeloid series with scattered foci of nucleated red cells. The sinusoidal endothelium was prominent. "Germinal centers" were preserved but less frequent than usual. The *liver* sinusoids contained less prominent foci of myeloid cells with some myelocytes, metamyelocytes and young neutrophils. Sections of *bone marrow* from various sites showed marked diffuse cellularity, mainly marked erythrocytic hematopoiesis with frequent foci of myeloid hematopoiesis. Megakaryocytes were numerous. Sections of other organs showed no significant findings.

The final *diagnoses* were: extramedullary hematopoiesis of the spleen (marked) and liver (moderate); marked splenomegaly; hyperplasia of the bone marrow; anemia; edema, hydrothorax, slight ascites and slight hydropericardium; cardiac dilation; splenic infarction; and uric acid calculus of the left kidney pelvis.

**Comment.** Myeloid metaplasia of the spleen has come to be recognized as a fairly frequent condition which may mimic various blood dyscrasias. The clinical features and autopsy findings of this case parallel those described as "agnogenic myeloid metaplasia of the spleen" by Jackson, Parker and Lemon.<sup>1</sup> A long series of experiments dealing with benzol (benzene) poisoning in the rabbit, carried on by Weiskotten and his associates,<sup>6-9</sup> has not showed a comparable degree of hematopoiesis in the rabbit spleen. However, toxicologic investigations<sup>2,3</sup> indicate that myeloid metaplasia of the human spleen frequently is associated with chronic benzol\* poisoning. Opinion has been expressed that a relationship between myeloid metaplasia and leukemia cannot be excluded.<sup>2,5</sup> Several other cases of myeloid metaplasia of the spleen studied in this department have presented similar autopsy findings and clinical courses easily confused with leukemia or various types of anemia. One of these cases had a history of exposure to a compound related to benzol. In the case reported, I know of no history of chronic exposure to benzol. The patient

\* The term "benzol" is used here in the sense of its usage by Mallory, Gall and Brickley,<sup>2</sup> to mean the ordinary commercial benzol rather than the chemically pure product (benzene).

received Fowler's solution during her initial polycythemic phase and radiation over the splenic area terminally.

**Summary.** Through 8 years, this patient had successively splenomegaly, erythremia, anemia, and blood smear and bone marrow characteristics of so-called subleukemic myelosis. At autopsy, extensive myeloid hematopoiesis of the spleen, moderate myeloid hematopoiesis of the liver, and bone marrow hyperplasia, particularly erythrogenic, were found. It was thought that these features perhaps represent successive stages of a single hematopoietic disorder of unknown etiology. Conditions associated with splenic myeloid metaplasia, such as chronic benzol exposure, are discussed. Gout was regarded as probably a coincidental feature.

#### REFERENCES

1. JACKSON, H., JR., PARKER, F., JR., and LEMON, H. M.: *New England J. Med.*, 222, 985, 1940.
2. MALLORY, T. B., GALL, E. A., and BRICKLEY, W. J.: *J. Indust. Hyg. and Toxicol.*, 21, 355, 1939.
3. RAWSON, R., PARKER, F., JR., and JACKSON, H., JR.: *Science*, 93, 541, 1941.
4. REIFENSTEIN, G. H.: *AM. J. MED. SCI.*, 197, 215, 1939.
5. STEWART, F. W.: Summary of Discussion, Third Conf. in Surg., Path., Div. of Lab. and Res., Albany, N. Y., Nov. 5, 1942, p. 7.
6. WEISKOTTEN, H. G.: *Am. J. Path.*, 6, 183, 1930.
7. WEISKOTTEN, H. G., GIBBS, C. B. F., BOGGS, E. O., and TEMPLETON, E. R.: *J. Med. Res.*, 41, 425, 1920.
8. WEISKOTTEN, H. G., SCHWARTZ, S. Cr, and STEENSLAND, H. S.: *J. Med. Res.*, 28, 127, 1915.
9. WEISKOTTEN, H. G., and STEENSLAND, H. S.: *J. Med. Res.*, 32, 215, 1917.

### PERIARTERITIS NODOSA

#### A CASE WITH AUTOPSY

BY LT. COL. RICHARD N. WASHBURN, M.C., A.U.S.

AND

MAJOR THOMAS O. OTTO, M.C., A.U.S.

APO 887, C/O POSTMASTER, NEW YORK, NEW YORK.

PERIARTERITIS nodosa is a relatively rare disease, described first by Kussmaul and Meier in 1866, and characterized pathologically by panarteritis of the medium-sized and small arteries throughout the body. The clinical symptoms, which are protean, depend upon the system which is the most affected in the development of the disease. The etiology is not definitely known, but the pathologic findings of polymorphonuclear and round cell infiltration in the adventitia and media of the affected vessels point toward an infectious basis. Recently Rich and Gregory have pointed out the rôle of hypersensitivity in the etiology of the condition.

The following case is reported because of its occurrence with rapidly fatal manifestations in a previously healthy young soldier who did not break down until after the stress of combat.

**Case Report.** A 21 year old artillery private, native of Washington, D. C., reported to his battalion surgeon on June 25, 1944, in France, complaining of abdominal pain and nausea, of a few hours duration. The patient had a fever

of 100° F. (37.8° C.). A diagnosis of acute appendicitis was made and the patient was evacuated to a clearing station. Operation was not performed and the patient was sent through the chain of evacuation to the United Kingdom, arriving at this hospital on July 6, 1944. The past history revealed nothing of significance except seasonal hay fever. The patient's complaints, 11 days after the onset of the initial symptoms, consisted of moderate pain in the upper right quadrant, moderate weakness, and anorexia. Physical examination revealed moderate emaciation, fever of 99.5° F. (37.5° C.), tenderness and a rather indefinite, deep, firm mass in the upper right quadrant of the abdomen, extending from the epigastrium to the right flank and 10 cm. below the costal margin. The heart and lungs were not remarkable. There was no lymphadenopathy nor edema of the extremities. Rectal examination revealed no abnormalities in the anus or lower rectum. The blood pressure was 138/84. The skin was normal.

*Laboratory Studies.* Roentgen studies of the chest, stomach, duodenum and colon revealed nothing remarkable. Proctoscopic examination revealed no ulcerations, polyps, or tumors in the descending colon. Stool examination and culture revealed no parasites or ova. A blood count on July 8 revealed the following: RBC 3,330,000, WBC 14,650 (neutrophils 88%, lymphocytes 12%), Hb 76% (11 gm.) (Sahli). Urine examination revealed normal findings.

In view of the secondary anemia blood transfusions of 500 cc. of compatible bank blood were given on July 13 and 15. In spite of the transfusions, blood studies on July 15, 1944, revealed RBC 3,120,000, Hb 70%, WBC 15,100 (neutrophils 90%, lymphocytes 10%).

The patient continued to complain of pain in the abdomen and did not improve under medical measures. On July 15, 1944, a laparotomy was performed, preceded by a transfusion of 500 cc. of compatible bank blood, and alkalization by means of sodium lactate. The tentative diagnosis before operation was subacute perforation of a duodenal ulcer or acute suppurative cholecystitis. Under gas-oxygen-ether anesthesia, with upper right rectus incision the following lesions were noted: the liver was markedly enlarged, the inferior margins rounded, extending 10 cm. below the costal margin. The enlargement involved all lobes and the palpable mass before operation was found to be the quadrate lobe. The capsule was smooth, glistening, and did not appear cirrhotic. The color was mottled red-brown, and darker than normal. There were numerous dense, fibrous adhesions between the dome of the right lobe and the diaphragm. The spleen was slightly enlarged, of normal consistency, and the margins rounded. The stomach, duodenum, kidneys, entire small and large intestine and appendix appeared normal. The mesentery and retroperitoneal lymph nodes showed no pathologic changes. The omentum was delivered from beneath the liver margin with difficulty after freeing pericholecystic adhesions. The gall bladder was moderately enlarged, thick-walled and the peritoneal surface was gray-white in color. The wall was edematous throughout and free from any evidence of gangrene or perforation. No calculi were palpated in the cystic or common ducts. In view of the obviously pathologic changes in the gall bladder, it was felt that the liver changes might be secondary to acute suppurative cholecystitis and cholecystectomy was carried out. Examination of the gall bladder after removal revealed a large thrombotic area situated intramurally in the posterior aspect opposite the ampulla. Gross section revealed no evidence of calculi, but the mucosa was of "strawberry" appearance with no evidence of necrosis. The wound was closed in layers and Penrose drainage was instituted from the foramen of Winslow. The patient evidenced mild shock postoperatively and whole blood was given during and immediately after the operation.

The postoperative convalescence was uneventful until the 7th day. The patient's temperature was normal 2 days after operation, pulse and respirations were normal, his appetite returned and he was anxious to get out of bed. On the 7th night the patient suddenly became dyspneic and orthopneic. Cyanosis was noted, and the superficial veins of the forehead and neck became engorged. Physical examination disclosed coarse râles and rhonchi throughout both lung



fields with dullness in both bases. The cardiac borders were slightly widened both to the right and left. The heart rate was rapid, the apex rate being 160. Blood pressure was 160/100. There was gallop rhythm. A roentgenogram of the chest next morning disclosed dilation of the right auricle and ventricle and marked passive congestion of both lungs. Rapid digitalization was carried out, oxygen therapy was instituted, and the usual treatment for cardiac failure given. Examination of the abdomen showed the operative wound to be intact and not infected. The liver border was palpated 8 cm. below the costal margin. The patient held his own on 8th day, the pulse rate dropping to 108, but the gallop rhythm persisted. There was marked diminution of râles in the lungs, and it was felt that he might survive. Next day the patient was brighter, the pulse was 100, gallop rhythm still present. An electrocardiogram disclosed changes characteristic of myocardial failure. The NPN of the blood was 60 mg./100 cc. of blood. At 1715 hours on the ninth post-operative day, while talking to a ward attendant who was feeding him, the patient suddenly expired.

**Autopsy** (2 hours after death). Only the significant findings are presented.

**Heart.** The epicardial surfaces were smooth and glistening. The right auricle was dilated to approximately 4 times normal size. The tricuspid valve was competent and there were no scars or vegetations present. The right ventricle was slightly dilated and the wall thickened slightly. The pulmonary valves were competent and the endocardial surfaces smooth. The endocardial surface of the right auricle was smooth and glistening. There were a few postmortem thrombi on the right ventricular wall. The left auricle was normal in size and appearance. The foramen ovale is closed. The left ventricle was normal in size and the endocardial surfaces smooth and glistening. The mitral valve was normal. There were a few small yellow plaques of atheroma in the region of the aortic ring. The aortic valves were normal. Cut surfaces through the interventricular septum and through the walls of the ventricles revealed a reddish gray surface, which was lighter in color than normal. The coronary arteries were grossly thickened on section and there were a few thrombi present in the anterior descending branch of the left coronary artery.

**Lungs.** Both lungs were edematous and boggy. There were no thrombi in the pulmonary vessels and the bronchi and bronchioles appear normal. In the left lower lobe, inferior surface, there was an area of recent hemorrhage measuring approximately 2 by 2 cm. No thrombus could be demonstrated in the efferent or afferent blood-vessels to this area.

**Liver.** The liver was markedly enlarged, rather soft in consistency, and the superior surface of the right lobe is adherent to the diaphragm by dense fibrous adhesions. The markedly enlarged left lobe was adherent to the spleen and the gastro-colic omentum by firm fibrous adhesions. The omentum was densely adherent to the gall bladder bed and to the inferior surface of the right and left hepatic lobes. When the liver was removed from the peritoneal cavity there were many areas of dense fibrous tissue radiating from foci of scarring in the capsule. Cut surfaces of the scarred areas in the capsule disclosed multiple round and oval-shaped areas of necrosis surrounded by definite capsules. These areas measured from 3 by 3 cm. to tiny areas of a few mm. in diameter. Most of the infarcts were subcapsular and were scattered throughout both right and left lobes. Branches of the hepatic and portal blood-vessels throughout the liver were thickened and in the left lobe there were well-organized thrombi in the largest branches of the portal vein. The intervening liver tissue between the necrotic areas appears essentially normal on examination.

**Spleen.** The spleen appeared normal in size and texture. Near the lower pole there were a few fibrous adhesions to surrounding structures. The cut surfaces revealed a dark red, rather firm parenchyma. There were no infarcts or necrotic areas in the spleen, nor evidence of hyperplasia of the pulp.

**Pancreas.** This organ appeared normal in size and color, but felt slightly more firm than normally. The splenic vessels were patent throughout.

*Adrenal Glands.* The right adrenal was markedly thinned-out and adherent by fibrous adhesions to the inferior aspect of the enlarged right lobe of the liver. No medullary tissue was present grossly and the cortex was approximately 1 mm. in thickness. The left adrenal appeared normal in size and texture and the cortical and medullary markings were well preserved.

*Kidneys.* The right kidney was smaller than normal. The perirenal fat was minimal and there were old scars on the capsule of the kidney. The kidney appears pale and softer in consistency than normal. The capsule stripped with difficulty and was adherent to the cortex by adhesions over the areas of scarring. Surfaces made by cutting revealed a gray cortex, narrower than normal, and in which there were multiple triangular-shaped areas of necrosis. The bases of the triangles were subcapsular while the apices were directed toward the pelvis. These areas varied in size from 2 to 4 mm. in their greatest extent. The medullary portion of this kidney was streaked with gray fibrotic laminae radiating from the pelvis. The pelvis is normal in size and studded with pin-point hemorrhages in the mucosa. The ureter was normal. The left kidney resembled the right and contained multiple subcapsular necrotic areas which produced scarring of the overlying capsule.

The *gastro-intestinal tract* appeared normal throughout.

The *inferior vena cava*, mesenteric vessels, and those branches of the portal system below the hepatic portion were patent throughout their walls and did not appear thickened.

MICROSCOPIC EXAMINATION (by Lt. Col. D. Murray Angevine, Medical Corps, A.U.S.).

*Lung.* The bronchioles are patent and slightly collapsed. The alveolar septa are moderately thickened by hyperemia and edema with considerable swelling of the epithelium. Most alveoli are filled with edematous fluid; many are filled by a hyaline-like membrane. In one section an extensive fresh intra-alveolar hemorrhage is seen, with a few adjacent alveoli filled by partly organized fibrin coagulum. Several small vessels contain unattached thrombi.

*Heart.* The subepicardial fat was extensively infiltrated with round cells. In the myocardium numerous slightly degenerated muscle cells are seen. Adjacent to several small branches of the coronary artery, the muscle cells are considerably degenerated with a slight round cell infiltration and vascularization of the interstitial tissue. In a large branch of the coronary artery the lumen is partly occluded by a recent thrombus, adherent to an eccentrically thickened hyalinized slightly degenerated intima containing considerable fresh hemorrhage. The adventitia and outer fringe of media is extensively vascularized and moderately infiltrated with round cells, plasma cells and a few eosinophils.

*Liver.* In one section is seen a large vessel completely filled by a laminated compact adherent thrombus, with organization of the periphery. The media and adventitia are moderately vascularized and slightly infiltrated with round cells. There is considerable centrilobular congestion and parenchymal degeneration in the adjacent tissue. A similarly affected vessel, with more extensive vascularization is observed in a second section, with an extensive centrilobular necrosis, containing many pigment-laden histiocytes.

*Gall Bladder.* The epithelium is extensively desquamated. In the fibromuscular layer the adventitia of every artery is considerably thickened by an extensive infiltration of eosinophils, leukocytes, monocytes and round cells and with moderate vascularization. In several vessels, the intima is slightly thickened, and the endothelial cells are distended and ballooned by intracytoplasmic perinuclear vacuoles.

*Cystic Artery.* One large and several smaller branches of the artery are observed, joined together by a granular-like tissue continuous with the thickened vascularized adventitia, and extensively infiltrated with eosinophils, and round cells. The large and few small branches are filled with thrombi. The intima is considerably thickened and vascularized in a few small vessels.

*Pancreas.* Numerous arteries are thickened and infiltrated similarly to those described in the liver and gall bladder. In a few small arteries the lumen is nearly occluded by a thickened intima.

*Adrenal.* In the periadrenal adipose tissue, several arteries are conspicuously thickened by a vascularized fibrosed adventitia and a greatly thickened hyalinized intima.

*Kidney.* In one section an area of coagulation necrosis is observed in the cortex adjacent to the capsule. The adventitia of the interlobular arteries is infiltrated with round cells and vascularized. In many the intima is thickened and the lumen narrowed. An interlobular artery is filled with a recent thrombus.

**Comment.** (Lt. Col. Angevine). "The extensive visceral vascular lesions, confined to the medium-sized arteries and affecting mainly the adventitia, indicate that this is a case of periarteritis nodosa. The almost complete involvement of the gall bladder vessels is an interesting finding in relation to the clinical history of suspected cholecystitis. The vascularity and extensive inflammatory exudate with moderate fibrosis are consistent with an early stage of the disease. The case will be coded as: periarteritis nodosa, early."

**Summary.** A fatal case of periarteritis nodosa with vascular lesions in several viscera has been presented. Nothing was brought to light as to the etiology. The history of hay fever might be significant in view of the recent work of Rich and Gregory. The remarkable feature of this case is the absence of symptoms until shortly before the final illness.

#### REFERENCES

RICH, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa, *Bull. Johns Hopkins Hosp.*, 71, 123, 375, 1942.

RICH, A. R., and GREGORY, J. E.: The Experimental Demonstration That Periarteritis Nodosa is a Manifestation of Hypersensitivity, *Bull. Johns Hopkins Hosp.*, 72, 65, 1943.

---

### CALCIFIC AORTIC VALVULAR STENOSIS

BY LAWRENCE H. SOPHIAN, M.D.

SENIOR SURGEON (R) U.S.P.H.S.

U. S. MARINE HOSP., U.S.P.H.S., STATEN ISLAND, NEW YORK.

THE purpose of this communication is to report the occurrence of an unexpectedly large number of instances of calcific aortic stenosis among autopsies at a U. S. Marine Hospital, to present significant data concerning this condition, and to attempt an etiologic subdivision of the cases.

After a period of service, the author became aware of the strikingly increased incidence of deformities of the aortic valve in the material at this hospital compared with that seen in private and municipal hospitals. The material forming the basis of this paper—31 examples of fibro-calcific deformities of the aortic valve—was derived from 500 consecutive autopsies. Hall and Ichioka<sup>1</sup> also described 31 cases of the same type, but their autopsy volume is estimated at 4000 or more. Reich<sup>2</sup> reported 22 examples of aortic deformity with calcification (cases of mitral stenosis were excluded) derived from 8 years' post-mortem material at Kings County Hospital, a total of about 10,000 autopsies. No explanation is offered for the heightened frequency of the condition at the Marine Hospital; but factors of age, sex and occu-

TABLE 1.—CASES OF CALCIFIC AORTIC VALVULAR STENOSIS WITH PREDOMINANT RHEUMATIC PATHOLOGY

No.	Age	Race	Hist. of Rv.	Heart wt.	Anatomy of aortic valve	Histology of aortic valve	Other heart lesions	Other disease
800	45	Eng.	Yes	380	Cusps thick, edges rolled; adherent commissures; nodular calcification on margins	Spongiosa vascularized; hyaline scars and calcification in ventricularis	Aschoff bodies	Fracture of skull
838	43	U. S.	Yes	650	Cusps short and fused; rolled calcific edges and thick bands between cusps	Fibrinoid foci, vascular spongiosa with exudation	Mitral stenosis	
834	48	U. S.	Yes	800	Bicuspid deformity; thick cusp margins; calcified commissure	Hyaline scars in ventricularis; vascularization and calcification in spongiosa.	Mitral stenosis	Multiple infarcts
852	39	Ital.	Yes	680	Short adherent cusps, rolled edges, calcification in margins and bases.	Fibrinoid degeneration and hyaline scarring of spongiosa and ventricularis; new vessels and Aschoff bodies	Mitral stenosis	Multiple infarcts
860	47	U. S.	Yes	750	Calcified adherent cusps; nodular margins; warty masses on both surfaces	Vascularized spongiosa and hyaline scarred ventricularis; focal lymphocytes	Sl. mitral nodularity	Adv. arteriosclerosis
875	62	U. S.	No	1000	Short calcified cusps, adherent to aortic wall	New vessels and focal scars in aortic ring; perivascular mononuclears in spongiosa	Pericard. adhesions; mitral st.	
907	45	Span.	No	470	Fused and calcified cusps, rough nodular margins; fresh vegetations (monilia)	Hyaline vascularized ring; focal scars beneath ventricular surface	Old pericarditis	
1222	34	Negro	Yes	975	Short calcified cusps; thick nodular closure line, fusion of two cusps	Dense hyaline necrotic foci, vascularized ventricularis, perivascular exudate	Focal scars of myocard.	
956	44	U. S.	Yes	850	Cusps and ring form a rigid triangular opening; aortic and ventricular surfaces rough and calcified	Calcification in hyaline scar tissue; new vessels and lymphocytes present	Mitral stenosis; pericarditis	Pulmonary infarcts
1016	35	U. S.	Yes	750	Cusps short and adherent; calcification on ventricular surfaces	Ventricular hyaline with fibrinoid foci; new vessels and mononuclear infiltration	Sl. mitral nodularity; Aschoff bodies	
1057	56	U. S.	No	600	Roller edges, adherent commissures, with calcification at closure line	Subendocardial hyaline and fibrinoid degeneration; vascularization and mononuclear exudate	Sl. mitral thickening and narrowing	
1080	39	Norw.	Yes	900	Fusion of cusps by thick calcified commissures; edges rolled and nodular	Hyaline scars in ring and spongiosa; monocytes in perivascular foci	Mitral stenosis	
1092	67	U. S.	No	600	Bicuspid, with thick margins and calcification in sinuses; nodular and calcified mass on ventricularis of one cusp	Vascularization and perivascular mononuclear foci in spongiosa; hyaline scarring of ventricularis	Moderate mitral deformity	Cancer of bladder
1126	40	U. S.	Yes	610	Short cusps, calcified commissure, thick rolled margins	Hyalinized, fibrinoid foci in ring and cusps; new vessels and exudate in both spongiosa and ventricularis	Mitr. stenosis and pericarditis; Aschoff bodies	
1138	53	U. S.	Yes	900	Short cusps with calcified nodular ridge on ventricular surface	Aschoff bodies in spongiosa and fibrinoid subendocardial foci in ventricularis	Moderate mitral stenosis	
1158	49	Russ.	Yes	410	Cusps short and adherent; thick nodular margins; calcified masses in sinuses	Hyaline scars in ventricularis and spongiosa; foci of perivascular exudate	Mitral stenosis	
1167	47	U. S.	Yes	500	Bicuspid, nodular and calcified thick commissure; calcific masses in sinuses	Hyaline scars and calcification in ventricularis and vascularization and focal exudate in spongiosa	Mitral stenosis; Aschoff bodies	

TABLE 2.—CASES OF CALCIFIC AORTIC STENOSIS WITH PREDOMINANT PATHOLOGY OF MÜNCKENBERG'S SCLEROSIS

No.	Age	Race	Hist. of Hf wt.	Anatomy of aortic valve	Histology of aortic valve	Other heart lesions	Other disease
853	63	Ger.	No	Cusps rigid with calcification in sinuses and smooth cleuro lines	Atheroma and fibrosis in fibrosa; no vascularization	Interstitial scars	Glomerulonephritis
859	66	U. S.	Yes	Calcification of ring and cusps; calcific masses in sinuses	Scars and focal calcification in ring and fibrosa of valve; no exudate; spongy normal	Mod. mitral deformity	Cancer of lung
901	43	Swed.	No	Cusps fused and covered on aortic aspect by spiky calcareous masses	Fibrosis, calcification and osseous metaplasia in fibrosa of cusps and ring	Myocardial fibrosis	Situs inversus
914	74	Swed.	No	Calcification and shortening of cusps; nodular masses in sinuses	Lipoid and calcific changes in aortic wall and fibrosa of cusps; no exudate	None	Meningitis
938	51	U. S.	No	Calcification of proximal halves of cusps and aortic ring	Atheroma and calcification of intima and fibrosa; atrophy of spongiosa; no exudate	None	Uremia
980	70	U. S.	Yes	Calcific masses on both sides of cusps; fusion of commissures; calcified ring	Intimal degeneration and focal calcification; fibrosa involved; no vascularization	Myomatous; coronary sclerosis	
997	53	U. S.	No	Calcified nodular commissure with masses in sinus; rigid calcific cusps	Hyaline fibrosis and calcification in fibrosa and ring; no vascularization or exudate	Myocard. scars	Diabetes
999	50	Norw.	No	Atheromatous and calcific mass on commissure	Intimal degeneration and lipoid deposit; focal calcification; no vascularization	None	Ca. bladder; uremia
1027	43	U. S.	No	Calcific nodule on sinus surface of a commissure; cusp margins smooth and sharp	Intimal atheroma with foci of calcification in fibrosa; no new vessels or exudate	None	Fracture of spine
1071	68	Norw.	No	Nodular calcification on commissures, fusion of cusps; margins and edges smooth	Atheroma and calcification in aortic intima and fibrosa of cusps; spongy normal	None	
1144	70	Swed.	No	Calcified plaques in sinus extending onto aortic surfaces of cusps	Atheroma of aortic intima; fibrosis in stroma of cusps; no vascularization or exudate	None	Diabetes
1227	78	U. S.	No	Calcified fused commissure with nodular masses in sinus; thin cusp edges	Atheroma and calcification in aortic intima and fibrosa of cusps; no vascularization	None	Cancer of mouth
1243	49	Negro	Yes	Cusps rigid and adherent to aortic wall; calcification on aortic aspect in sinuses	Atheroma, hyaline fibrosis and calcification in fibrosa; no vascular or perivascular lesions	Mitral thickening	Syphilis
1271	51	Negro	No	Atheroma and plaques of calcification on aortic side of cusps; thick fused commissure	Aortic intima and fibrosa of cusps show hyaline foci atheroma and calcification	None	Cancer of lung

pation are suspected. Our patients are predominantly male adults and a high proportion are seamen. Scandinavians are much more numerous than in the population at large. The average age of our deceased patients is 49 years.

TABLE 3.—ANALYSIS AND INCIDENCE OF CALCIFIC AORTIC STENOSIS IN 500 AUTOPSIES

Total valvular heart diseases . . . . .	57
Cases of calcific aortic stenosis . . . . .	31
Number of these showing mitral endocarditis . . . . .	17
Etiology of calcific aortic stenosis by pathologic criteria:	
Entirely or predominantly rheumatic . . . . .	17
Associated with severe arteriosclerosis . . . . .	1
Entirely or predominantly atherosclerotic . . . . .	14
Associated with diabetes . . . . .	2
Associated with rheumatic lesions . . . . .	2

The inclusion with our cases of instances in which other valves besides the aortic were diseased was decided upon because the two principal etiologic bases are rheumatic fever and arteriosclerosis. Since in the age group under consideration both of these diseases are frequent, it was obvious that all examples of aortic stenosis should be included, both with and without involvement of other valves by the same or another process. In these 500 autopsies there were found 57 hearts with valvular diseases, excluding only the characteristic aortic deformity associated with luetic aortitis. Of these cases, 40 showed varying degrees of mitral stenosis, and 31, including some of the mitral stenosis cases, showed calcific aortic stenosis. A further analysis of the types of aortic valvular damage is made in Tables 1 and 2, and a summary of the conditions found and their association with one another appears in Table 3.

After tabulating the cases and enumerating the anatomic and histopathologic details in each, it became apparent that a decision was required concerning the significance of several of the observations before a pathogenetic classification could be accomplished. Hall and Anderson<sup>3</sup> and Karsner<sup>4</sup> have reported that a majority of all hearts show typical rheumatic lesions if carefully examined for them. Therefore it has seemed to us that the use of rheumatic stigmata of the pericardium, myocardium and other cardiac valves as a basis for deciding upon the etiology of calcific aortic stenosis is unreliable. A better way to determine the rheumatic etiology of aortic valve lesions is to find the specific anatomic and histopathologic changes in the cusps and ring of the aortic valve itself. On this basis the 17 cases in Table 1 have been classified as rheumatic and the 14 cases in Table 2 as sclerotic.

The lesions included in Table 1 are variable in severity, reducing the aortic orifice moderately or severely. In some there are flat calcific plaques in the sinuses of Valsalva, thickening and stiffening the aortic cusps. In others this is combined with massive calcific nodules, or spiky encrustations on both aortic and ventricular surfaces of the cusps, sometimes with erosion of the intima and deposition of

fibrin thrombi. Fusion of the cusps is of variable severity, and results in the formation of a dense triangular diaphragm or a false bicuspid



FIG. 1.—Case 1092. Classified as rheumatic in etiology because of the bicuspid type of deformity, with thick rolled eusp margins (seen where the clamp is attached) and the histologic pathology. Moderate mitral valve deformity is present.



FIG. 2.—Case 956. Nodular calcification of all aortic cusps with the formation of a rigid funnel-shaped orifice. This heart showed mitral stenosis and histologic evidence of old rheumatic inflammation.

valve. The commissural lesions are broad and dense. The margins of the cusps and the closure line are least affected. Histologically the intima of the sinuses and cusps is thickened by edema and fibrillary

reduplication, with deposition of lipid material in the subendothelial tissue. Phagocytosis of the lipid occurs in plaques. The fibrosa of the cusps near their base becomes thickened and hyalinized. Foci of

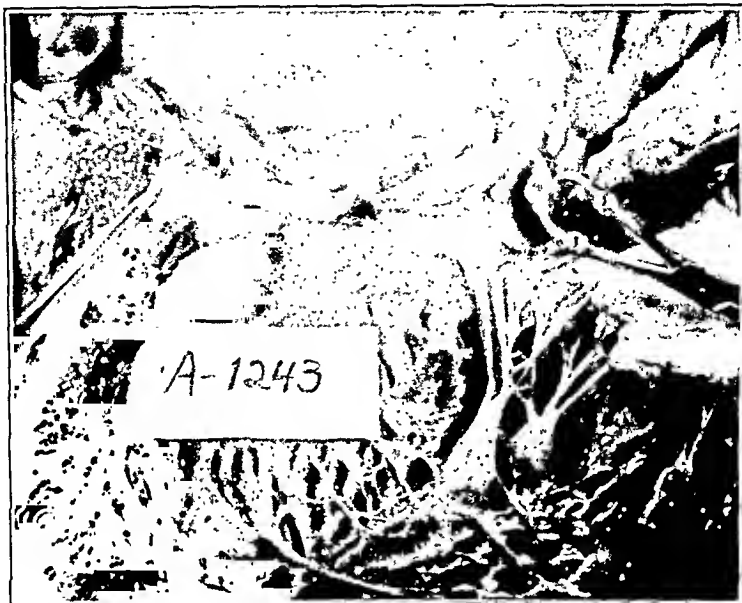


FIG. 3.—Case 1243. The cusps are rigid and partly fused by dense fibrosis in the commissures. Luetic aortitis is present but the histologic studies show that the valve deformity is sclerocalcific (Mönckeberg's type).



FIG. 4.—(This case is not in the series because there is no stenosis.) The early sclerotic and focally calcific thickening and degeneration seen at the cusp attachments to the aortic wall are regarded as the beginnings of Mönckeberg's sclerosis and are presented for comparison.



calcification occur in this layer and in the adjacent aortic ring. Osseous metaplasia is observed in some advanced lesions. The calcific masses impinge upon and may ulcerate through the ventricularis or arterialis of the valve. The spongiosa at the attachment of the cusp is usually narrow and shows few vessels and only a scattering of lymphocytes.

In Table 2 are listed the aortic deformities which in our judgment have the gross and microscopic appearances of rheumatic lesions. Many of them show considerable atheromatous degeneration and sclerosis superimposed upon the primary process. Although again there is wide variation in degrees of deformity, the usual lesion consists of shortening and thickening of the cusps in their distal portions, with nodularity along the closure line. The margins are rolled or inverted. The commissures are bridged by light fibrous bands. Bicuspid deformity is produced by intimate fusion of adjacent cusps, leaving a low fibrous ridge in the combined sinus of Valsalva thus formed. The histopathology is that of rheumatic fever. The principal features are Aschoff bodies, fibrinoid degeneration (with material present taking fibrin stains), arteriolar necrosis or disorganization, peri-capillary or peri-arteriolar exudation of lymphocytes and cardiac histocytes, and focal hyaline acellular scars. The sub-endocardial layer of the ventricular surface of the cusps and the spongiosa at the base of the cusps are characteristically the sites most involved.

The age incidence in the two groups is in a range from 43 to 78 years in the sclerotic, and 34 to 67 in the rheumatic cases. All were males. A history of an illness or symptom of the types generally recognized as associated with rheumatic infection was obtained in 13 of the 17 cases grouped as rheumatic on anatomico-histologic grounds, and in 3 of the 14 cases in which the aortic deformity was classified as sclerotic.

Disease of the pericardium, myocardium or valves other than the aortic was found in a considerable number of the cases. The chief coincidence was that of mitral stenosis. Ten of the 17 rheumatic aortic cases showed mitral stenosis. Of the 14 sclerotic aortic stenoses, 2 hearts showed moderate or severe mitral deformity, and 1 showed luetic type of infiltration and elastic tissue destruction in the aortic root as well as in the descending aorta. A summary of these figures appears in Table 3.

**Discussion.** For the past century clinicians and pathologists have been attempting to affirm the etiology and pathogenesis of fibro-calcific stenosis of the aortic valve, beginning with Hasse in 1846,<sup>5</sup> who believed that either endocarditis or atheromatous degeneration could be responsible. Mönckeberg<sup>6</sup> in 1904 described a type of aortic stenosis which he believed was due to primary sclero-calcific degeneration, beginning as plaques in the sinus pockets and ascending toward the free border of the valve cusps. The primary histopathologic lesion was described as sclerosis and calcification of the fibrous matrix of the valve. Further descriptions of calcific aortic stenosis of this type were given by Libman<sup>7</sup> and Ribbert.<sup>8</sup>

A number of modern authorities believe that rheumatic infection

is the principal, if not the exclusive, cause of aortic valvular deformities resulting in calcification and stenosis. Christian<sup>9</sup> described 21 cases in which the aortic valve alone was diseased and decided that the great frequency of a history of rheumatic manifestations (13 of the 21 cases) was significant and that "the etiologic relation of this lesion to rheumatic fever is very probable." Clawson, Noble and Lufkin<sup>10</sup> favor a rheumatic etiology for aortic stenosis in all cases as a result of a pathologic study of their material. Dry and Willius<sup>11</sup> came to the same conclusion on clinical grounds after studying a large series of cases, and offered the opinion that in calcific aortic stenosis the rheumatic infection was mild and prolonged. Hall and Ichioka<sup>1</sup> made a minute histo-pathologic study of cases of calcific aortic stenosis both with and without other valvular disease, and found support for the belief that rheumatic fever is the common background of all of them. Similar investigations were made by Karsner and Koletsky,<sup>12</sup> and resulted in the same conclusion.

Other investigators of this subject have been able to find examples of both rheumatic and sclerotic deformities of the aortic valve in their material (Margolis, Ziellessen and Barnes<sup>13</sup>). The group of cases studied by Sohval and Gross<sup>14</sup> was found by their criteria to include 32 examples of rheumatic endocarditis, of which 19 were multivalvular, and 18 instances of Mönckeberg's aortic valvular sclerosis. In the latter group 3 cases showed some rheumatic stigmata in one or another part of the heart, and 4 showed syphilis of the aorta. These authors concluded that Mönckeberg's sclerosis of the aortic valve is distinguishable from rheumatic disease, and suggested that deformity of the valve by any disease is possibly a predisposing cause of the former process.

One of the arguments advanced against the existence of primary calcific sclerosis of the aortic valve is the observation that arteriosclerosis is usually of slight degree in the adjacent aorta. This, however, may be regarded as a phenomenon resulting from the protective effect of the aortic stenosis on the adjacent aortic wall, shielding it from the force of the blood flow. Such an effect is observed in peripheral arteries, where the wall beyond a calcified plaque is frequently found free of atheromatous degeneration. On the other hand, the aortic wall at a point opposite the valve orifice frequently shows a sclerotic plaque, marking the zone of impact of the narrow stream of blood formed by the stenosis. Hall and Ichioka<sup>1</sup> make reference to this, and call it an "impingement" plaque.

If then the aorta is usually not markedly sclerotic, one may ask how does Mönckeberg's sclerosis of the aortic valve develop, since it is stated to be a process originating in the aorta? This is only an apparent rather than a real objection, since the point of origin is not the aorta in general but that small portion within the sinuses of Valsalva along the insertion margins of the cusps. In this area all of our cases show atheromatous degeneration and calcification. The underlying causes of these changes may be any combination of mechanical, toxic, metabolic and infective phenomena allegedly associated with arteriosclerosis (Leary<sup>15</sup>). The exposed position of the aortic cusps, their

rapid to-and-fro flexion in the blood stream and the fixed position of the aortic ring where the sinuses of Valsalva receive the full impact of the regurgitant force after each systole are basic facts. The additional stress which may result from the presence of congenital bands or cusp deformities, or from inflammatory thickening or adhesions must also be considered. Some authors (Libman,<sup>7</sup> Reich<sup>2</sup>) believe that calcific aortic stenosis sometimes results from the healing of vegetative endocarditis. In the present group of cases, no example of this sequence of events has been recognized.

**Summary.** The great frequency of gross and histologic lesions of a type generally recognized as rheumatic but occurring in the absence of notable deformity, seems to us to invalidate an assumption that any coincident lesion necessarily has a rheumatic etiology. In this study of 31 cases there has purposely been no attempt to exclude those in which other valvular lesions were present as well as calcific aortic stenosis. The most frequently co-existent lesion was mitral stenosis (55%). Rheumatic aortic valvular disease was found in some cases in which no other cardiac lesion could be detected. Mönckeberg's sclerosis of the aortic valve was found in 2 hearts in which the mitral valves revealed definite evidence of inactive rheumatic inflammation, and in 1 in which syphilitic aortitis was present.

**Conclusion.** Thirty-one cases of calcific aortic valvular stenosis occurred in a series of 500 consecutive autopsies. Pathologic studies lead us to the belief that 17 were rheumatic in etiology and the rest are examples of Mönckeberg's sclerosis of the aortic valve.

#### REFERENCES

1. HALL, E. M., and ICHIOKA, I.: Etiology of Calcified Nodular Aortic Stenosis, *Am. J. Path.*, **16**, 761, 1940.
2. REICH, N. E.: Calcific Aortic Valve Stenosis, *Am. Int. Med.*, **22**, 234, 1945.
3. HALL, E. M., and ANDERSON, L. R.: Incidence of Rheumatic Stigmas in Non-rheumatic Hearts, *Am. J. Path.*, **18**, 778, 1942.
4. KARSNER, H. T.: Discussion of Hall and Anderson's paper, *Am. J. Path.*, **18**, 778, 1942.
5. HASSE, C. E.: *An Anatomical Description of the Organs of Circulation and Respiration* (trans. by W. E. Swaine), London, New Sydenham Society, p. 134, 1846.
6. MÖNCKEBERG, J. G.: Der normale histologische Bau und die Sclerose der Aortenklappen, *Virehows Arch. f. path. Anat.*, **176**, 472, 1904.
7. LIBMAN, E.: Some General Considerations Concerning Affections of the Valves of the Heart, *Med. Clin. North America*, **1**, 573, 1917.
8. RIBBERT, H.: In Henke, F., and Lubarsch, O., *Handb. d. spez. path. Anat. and Hist.*, Berlin, J. Springer, **2**, 195, 1924.
9. CHRISTIAN, H. A.: Aortic Stenosis With Calcification of the Cusp: A Distinct Clinical Entity, *J. Am. Med. Assn.*, **97**, 158, 1931.
10. CLAWSON, B. J., NOBLE, J. F., and LUPKIN, N. H.: The Calcified Nodular Deformity of the Aortic Valve, *Am. Heart J.*, **15**, 58, 1938.
11. DRY, T. J., and WILLIUS, F. A.: Calcareous Disease of the Aortic Valve: A Study of Two Hundred and Twenty-eight Cases, *Am. Heart J.*, **17**, 138, 1939.
12. KARSNER, H. T., and KOLETSKY, S.: Calcific Sclerosis of the Aortic Valve, *Trans. Assn. Am. Phys.*, **55**, 188, 1940.
13. MARGOLIS, M. H., ZIELESSEN, F. O., and BARNES, A. R.: Calcareous Aortic Valvular Disease, *Am. Heart J.*, **6**, 349, 1931.
14. SOHYAL, A. R., and GROSS, L.: Calcific Sclerosis of the Aortic Valve, *Arch. Path.*, **22**, 477, 1936.
15. LEARY, T.: Atherosclerosis, *Arch. Path.*, **21**, 419, 1936.

## A TENTATIVE TEST FOR PHEOCHROMOCYTOMA\*

BY GRACE M. ROTH, Ph.D.

SECTION ON CLINICAL PHYSIOLOGY

AND

WALTER F. KVALE, M.D.

DIVISION OF MEDICINE, MAYO CLINIC

ROCHESTER, MINNESOTA.

PAROXYSMAL hypertension and associated symptoms characteristic of the clinical syndrome caused by pheochromocytoma frequently have been described and are well known; but the differentiation from such clinical conditions as coronary occlusion, hyperthyroidism, histamine cephalgia, migraine, menopausal states and anxiety states, patients who are hyper-reactors, and patients who have persistent hypertension may be difficult. The most confusing cases, in our experience are the hyper-reactors and those in which the patients have essential hypertension and whose blood pressure is extremely labile. Patients who have anxiety states also cause difficulty because of their frequent description of attacks or spells of various kinds of symptoms.

In the past the diagnosis of suspected pheochromocytoma was confirmed by the attacks which characterized this clinical entity. These attacks, which might be either spontaneous or induced, were precipitated by various means including physical exertion, change in position such as rising from the recumbent to the upright position, turning on the side of the tumor, massage of the abdomen on the side of the tumor, immersion of the extremities in cold water or administration of insulin or epinephrine. Since none of these methods of inducing attacks is dependable and since the opportunity to observe the patient in a spontaneous attack may not present itself, it is apparent that a simple procedure that would induce attacks at will would be of great help in diagnosis.

Beer, King and Prinzmetal,<sup>1</sup> in 1937, and Hyman and Mencher,<sup>5</sup> in 1943, were able to demonstrate an epinephrine-like pressor substance in the blood of several patients during attacks caused by pheochromocytomas. Since attacks owing to such a tumor are similar to those produced by large injections of epinephrine and since large amounts of epinephrine have been extracted from many of the tumors investigated, it is logical to suggest that the attacks are due to sudden massive discharges of epinephrine from the tumor into the circulation.

Hyman and Mencher<sup>5</sup> also produced attacks of paroxysmal hypertension by the cold pressor test and by the injection of histamine. However, they failed to mention whether they considered the latter a suitable means for voluntary production of an attack.

In 1939, Horton and one of us (G. M. R.)<sup>4</sup> demonstrated an epinephrine-like response in the case of a patient who was hypersensitive to cold subsequent to a histamine-like response to the immersion of one hand in cold water. Also, Best and Taylor,<sup>2</sup> in 1943, reported

\* Read before the Central Society for Clinical Research, Chicago, Nov. 3, 1944.

that histamine and epinephrine are antagonistic in their effects on the capillaries and blood pressure.

As a result of these observations, an intravenous infusion of histamine was given to a patient in whom the diagnosis of pheochromocytoma was made in order to determine whether this drug could be used later during operation to counteract the increase of blood pressure which usually occurs during the surgical procedure. Each time the infusion was started, irrespective of the rate of flow, an attack was induced which was identical with the patient's spontaneous attacks. Small amounts of histamine base injected at another time produced similar attacks. Since it seemed possible that this procedure might be used as a test for pheochromocytoma, the present study was begun.

Since the importance of early diagnosis in cases of pheochromocytoma, methods of localizing the tumor, type of surgical procedure, anesthetic agent, and care of the patient before and after operation have been stressed on numerous occasions, no attempt will be made to elaborate on these subjects. Our purpose is to present a simple clinical test which we believe will precipitate an attack of paroxysmal hypertension in a patient who has pheochromocytoma. A preliminary report on the test has been published previously.<sup>7</sup>

**Method of Study.** *Selection of Subjects.* Fifty-one persons were divided into four groups, as follows: Group 1, 9 normal persons whose ages ranged from 20 to 48 years. Group 2, 22 hyper-reactors to the cold pressor test, whose ages ranged from 19 to 59 years. The basal blood pressure of the patients in Group 2 was less than 140 mm. of mercury systolic and 90 mm. diastolic; the rise of blood pressure during the cold pressor test was more than 22 mm. of mercury systolic and 15 mm. diastolic. Group 3, 16 patients who had well-established hypertension whose ages ranged from 32 to 62 years. The basal blood pressure was more than 140 mm. of mercury systolic and 90 mm. diastolic. Group 4, 4 patients who were suspected of having a pheochromocytoma with ages ranging from 39 to 59 years.

*Procedure.* The test as employed consisted of placing the person in a recumbent position for 30 minutes or until the blood pressure and pulse rate had attained or approximated the basal level. Before injection, in order that psychic stimuli could be ruled out, the patient was told the sequence of events to expect from the injection. With the blood pressure cuff on one arm, 0.05 of histamine base in 0.5 cc. of normal saline solution or 0.025 mg. in 0.25 cc. of normal saline solution was injected intravenously into the opposite arm. Readings of blood pressure and pulse rate were made at intervals of 1 minute for from 10 to 15 minutes. Both subjective and objective symptoms were noted. In addition, a cold pressor test was done on each person.

**Results.** *Group 1.* After injection of histamine, most of the 9 normal persons had only slight flushing of the face and mild headache which frequently disappeared at the end of 5 minutes. The blood pressure first decreased and then increased from the basal level to the approximate elevation obtained during the cold pressor test. The basal blood pressure ranged from 95 to 130 mm. of mercury systolic and from 65 to 74 mm. diastolic. The systolic blood pressure during the cold pressor test ranged from 112 to 150 mm.; during the histamine test it ranged from 110 to 150 mm. The diastolic blood pressure during the cold pressor test ranged from 70 to 85 mm. of mercury; during the histamine test it ranged from 64 to 74 mm. The

average rise of blood pressure during the cold pressor test was greater than that during the histamine test (Table 1). The results of the histamine test were regarded as negative. Figure 1, *left*, shows the response of a normal person to the intravenous injection of histamine and to the cold pressor test.

TABLE 1.—AVERAGE ELEVATION OF BLOOD PRESSURE AFTER THE COLD PRESSOR TEST AND AFTER THE INTRAVENOUS INJECTION OF 0.05 MG. OF HISTAMINE BASE

Cases	Classification of patients	Average blood pressure, mm. of mercury				
		Basal	During cold pressor test	During histamine test	Increase during cold pressor test	Increase during histamine test
9	Group 1: normal	109/70	127/87	124/77	18/17	15/7
22	Group 2: hyper-reactive	120/78	157/104	149/88	37/26	29/10
16	Group 3: hypertensive	162/104	202/125	198/118	40/21	36/14

*Group 2.* Twenty-two patients who were hyper-reactors to the cold pressor test had flushing of the face and headache after injection of histamine. These reactions were similar to those of the normal persons in Group 1. In 1 instance, histamine cephalgia developed as a result of the injection of histamine. The basal systolic blood pressure ranged from 100 to 130 mm.; the basal diastolic pressure ranged from 60 to 95 mm. During the cold pressor test the systolic blood pressure ranged from 132 mm. of mercury to 202 mm. and the diastolic ranged from 88 to 114 mm.; during the histamine test the systolic blood pressure ranged from 118 to 180 mm. and the diastolic blood pressure ranged from 64 to 120 mm. As in Group 1, the average rise of blood pressure during the cold pressure test was greater than that during the histamine test (Table 1). The results of the histamine test were considered to be negative. Figure 1, *right*, shows the response of one patient in Group 2 to the intravenous injection of histamine and to the cold pressor test.

*Group 3.* Sixteen patients who had well-established hypertension had more severe headaches after injection of histamine than were experienced in the previous group. These headaches rarely disappeared before 10 minutes and in some instances lasted 15 minutes. Circumoral pallor occurred in 6 cases. The average increase from the basal pulse rate of 78 beats per minute was 39 beats per minute. The average rise of blood pressure from the basal level was greater during the cold pressor test than during the histamine test (Table 1). Figure 2 shows the response of 1 patient in Group 3 to the intravenous injection of histamine and to the cold pressor test. Since no subjective symptoms other than tachycardia, circumoral pallor in 6 instances and headache occurred after injection of histamine, the results were regarded as negative.

*Group 4.* In contrast to the cases in the first three groups, in 3 of the 4 cases in which the patients were suspected of having a pheochromocytoma a definite attack was produced by the injection of histamine.

Since the first case already has been reported,<sup>6</sup> only features particularly important to the present discussion are included here. The other 3 cases are described in detail.

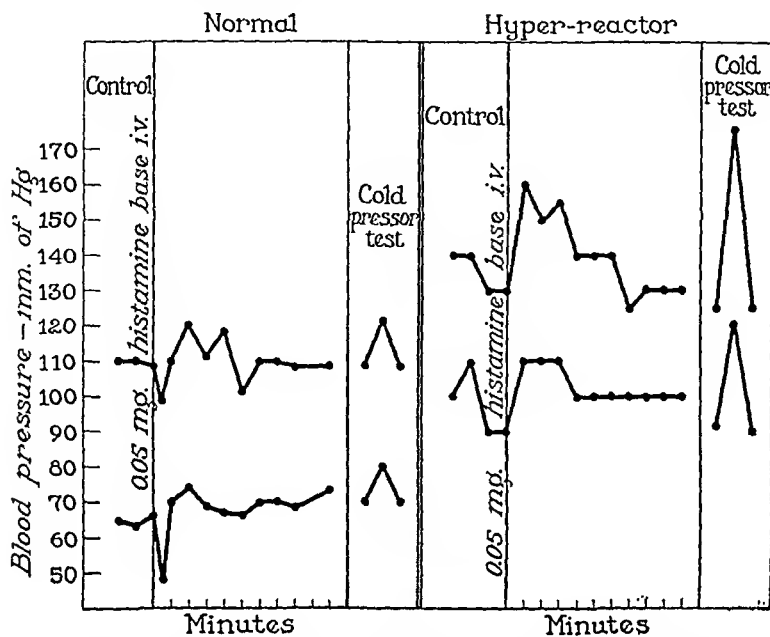


FIG. 1.—Left, blood pressure response of a normal person to the intravenous injection of 0.05 mg. of histamine base and to the cold pressor test. Right, blood pressure response of a hyper-reactor to the intravenous injection of 0.05 mg. of histamine base and to the cold pressor test.

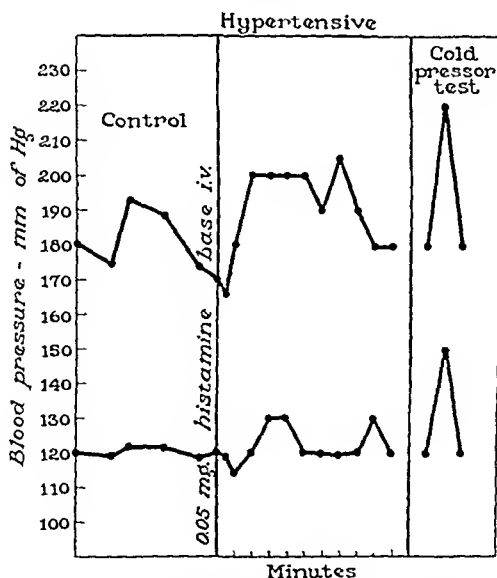


FIG. 2.—Blood pressure response of a patient who had hypertension to the intravenous injection of 0.05 mg. of histamine base and to the cold pressor test.

**Report of Cases.** CASE 1. In this case, that of a woman aged 41 years, attacks could be precipitated by exercise, change of posture and abdominal

massage. They were not precipitated by the cold pressor test, subcutaneous injection of 15 units of insulin, 1 cc. of 1:100,000 dilution of epinephrine or an intravenous infusion of 1 to 2 mg. of acetyl- $\beta$ -methyleholine chloride (meholyl ehloride) during 15 minutes, but they were precipitated by an intravenous injection of histamine. An attack was induced on one occasion by slow infusion of histamine and on 4 occasions by rapid intravenous injections of either 0.05 mg. or 0.025 mg. of histamine. After surgical removal of the tumor, the same test produced no significant change in blood pressure.

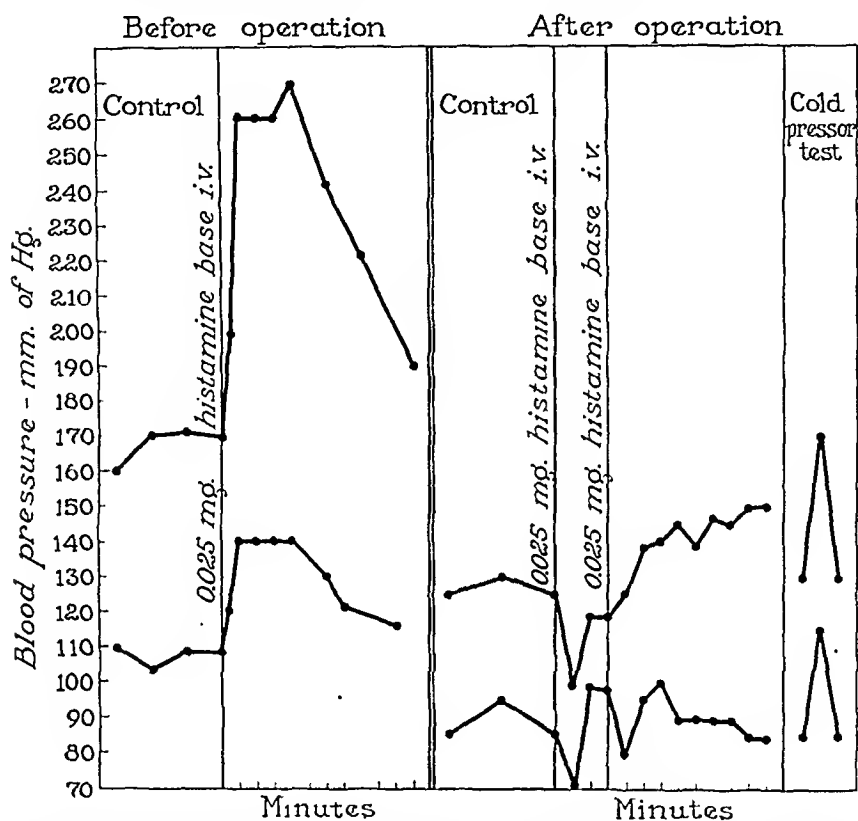


FIG. 3.—Blood pressure response of a patient who had pheochromocytoma (Case 2) to an intravenous injection of 0.025 mg. of histamine base before and after operation and to the cold pressor test.

**CASE 2.** A man, 59 years of age, was admitted to the Mayo Clinic on Nov. 5, 1943. For the last 3 years he had had attacks from 1 to 10 times a day. The attacks were always sudden in onset and generally lasted from 10 to 15 minutes. They were characterized by a generalized ill feeling, anxiety, fright, marked distress through the abdomen and chest, palpitation, headache which was not particularly severe, numbness of the left hand and arm and blanching of the left second and third fingers and left second and third toes.

The results of physical examination were not significant. The mean blood pressure over a period of 24 hours was 170 mm. of mercury systolic and 110 mm. diastolic. There was narrowing and sclerosis, Grade 2, of the retinal arterioles with a few small retinal hemorrhages. The grading was on the basis of 1 to 4, in which 1 represents the least and 4 the greatest degree. The only positive laboratory finding was evidence of mild renal insufficiency and a stone in the pelvis of the right kidney.

Before the patient came to the Mayo Clinic, the home physician observed him in several attacks which were induced by pressure on the left side of



the abdomen. Apparently the attacks also could be induced by bending the body to the left or by straining at stool. Likewise under our observation, the blood pressure rose from 140/100 to 264/148 on 1 occasion after an attack induced by pressure on the left side. A similar attack occurred, produced by the administration of histamine, in which the blood pressure rose from 170/140 to 260/140 (Fig. 3).

Because these attacks could be induced by pressure on the left side of the abdomen and by the intravenous injection of histamine, we concurred in the diagnosis of left pheochromocytoma which was made by the physician in the patient's home locality.

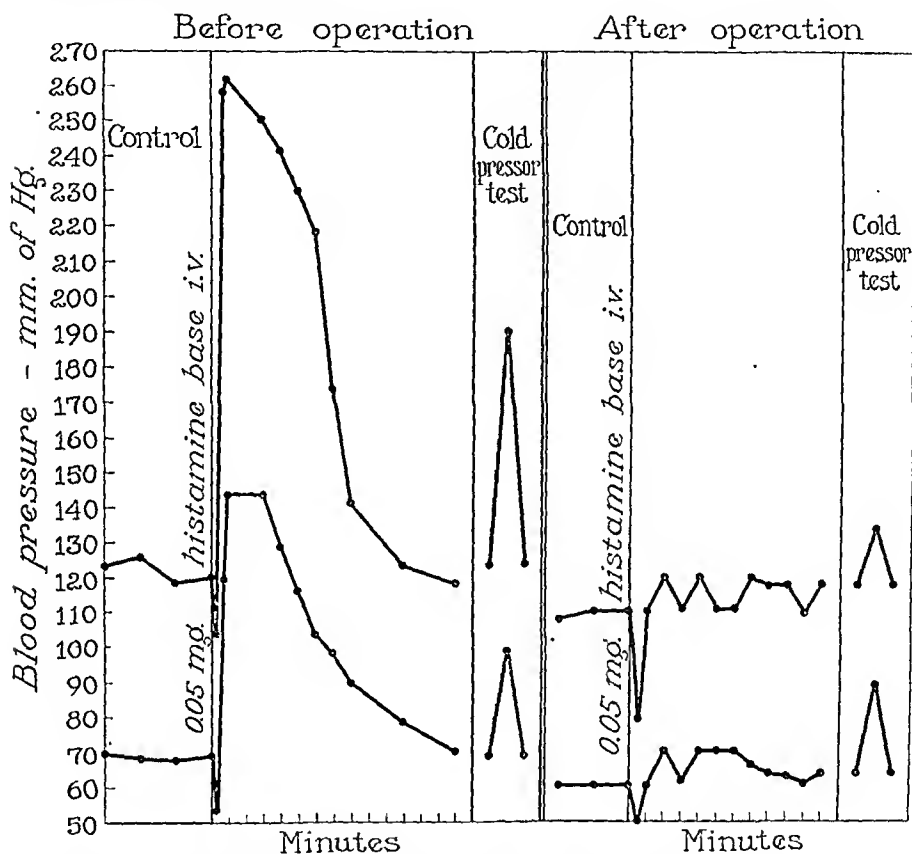


FIG. 4.—Blood pressure response of a patient who had pheochromocytoma (Case 3) to an intravenous injection of 0.05 mg. of histamine base before and after operation and to the cold pressor test.

On Nov. 19, 1943, the left suprarenal region was explored but no tumor was found; the wound was closed, the patient turned over, the right suprarenal region explored, the tumor located immediately and removed easily. The patient's convalescence was uneventful and he was dismissed from the hospital on the 15th postoperative day. The result of repetition of the histamine test on the 16th postoperative day was negative.

CASE 3. A man, 59 years of age, was admitted to the clinic on July 3, 1944, complaining of headaches of only 6 weeks' duration. These headaches usually occurred after the act of voiding. They were severe, sudden in onset, and were associated with considerable epigastric pain extending through to the back and up to the chest. In addition, there was palpitation and blurring of vision, sometimes to complete blindness. These attacks occurred from 1 to

4 times a day and lasted from 4 to 5 minutes. The patient had noticed some dull intermittent pain in the right loin, but this was not related to the urinary tract and was not associated with the attacks. He had had diabetes mellitus for 15 years.

The results of *physical examination* were essentially negative. The blood pressure was 110 mm. of mercury systolic and 80 mm. diastolic.

*Ophthalmoscopic examination* showed narrowing and sclerosis of the retinal arterioles, Grade 1. The results of laboratory studies were negative except for a fasting blood sugar of 274 mg. per 100 cc. of blood.

During the time the patient was studied in the hospital, he was observed in one attack after he had voided. No blood pressure readings had been obtained just prior to the attack but the readings always had been within normal limits. One minute after the attack started the blood pressure rose to 250/170; in 2 minutes it was 270/122 and in 10 minutes it had dropped to 135/80.

Two attacks were induced by the intravenous injection of 0.05 mg. and 0.025 mg. of histamine, respectively. The patient informed us that these attacks were identical to his spontaneous attacks and complained of a pounding, excruciating headache and severe epigastric pain extending to the back and chest. He was frightened and refused to lie quietly on the bed. In the first attack, the blood pressure rose from a basal level of 118/60 to 260/142. The attack subsided in 10 minutes, at which time the blood pressure was again normal (Fig. 4).

The diagnosis was pheochromocytoma. Because these tumors occur most frequently on the right side of the body,<sup>3</sup> and because the patient had had vague pains through the right flank, it was decided to explore this side first. Accordingly, on July 18, the right suprarenal region was explored, but no tumor was found. The incision was closed, the patient turned over and the left side explored, and the tumor found at the upper pole of the left kidney and successfully removed. The first 3 postoperative days were stormy, but thereafter convalescence was without incident. The result of the histamine test on the 17th postoperative day was negative. The patient was dismissed on the 19th postoperative day.

**CASE 4.** A dentist, 39 years of age, was admitted to the clinic on June 21, 1944, complaining of attacks of tachycardia and flushing of the face of 3 months' duration. These attacks, of which he had had 4, lasted about  $\frac{1}{2}$  hour. There was no associated pain but the attacks were annoying to the patient.

The results of *physical and laboratory examinations* were negative except for a mass in the left upper quadrant of the abdomen. This mass was considered to be the spleen. The diagnosis was indeterminate but the probability of a pheochromocytoma was considered. An attempt was made to induce an attack by injection of histamine but the reaction was unlike the symptoms of which he complained and the histamine test was negative. The patient was informed that the possibility of his having a pheochromocytoma was remote, but because of the mass in the left upper quadrant of the abdomen, he chose to undergo an abdominal exploration.

On July 27, exploration was undertaken through a primary upper right rectus incision. The spleen was slightly enlarged, but the results of exploration of the liver, gall bladder, stomach, duodenum and both suprarenal regions were entirely negative. After operation the histamine test was again negative.

**Comment.** The histamine test was performed in 9 cases in which the persons were normal (Group 1) and in 42 cases (Groups 2, 3 and 4) in which differentiation of paroxysmal hypertension owing to a pheochromocytoma from various other clinical conditions was thought necessary. The results of the test were regarded as negative in 39 of the 42 cases. In 4 of these 39 cases in which an opportunity was presented for exploration of the suprarenal regions, no tumor was found.

Since May 1, 1943, we had the opportunity of observing 3 cases in

which a correct clinical diagnosis of pheochromocytoma was made. The rapid injection of small amounts of histamine produced attacks identical with the spontaneous attacks of which these patients complained, thus affording us the opportunity of observing them in attacks. An attack was induced 5 times in 1 case and twice in another; the other patient refused to allow us to induce more than 1 attack. In each attack the systolic and diastolic blood pressure rose markedly and then promptly returned to basal levels within 10 minutes, when the attack subsided.

In each of the 3 cases in which the results of the histamine test for pheochromocytoma were positive, the tumor was removed successfully and the patient was restored to normal health. The tumors yielded from 50 to 682 mg. of crystalline epinephrine. During the postoperative period of these patients, repetition of the histamine test gave negative results.

**Summary.** An intravenous injection of 0.025 mg. or 0.05 mg. of histamine base was given to 51 persons who were divided into four groups as follows: Group 1, normal persons whose ages ranged from 20 to 48 years; Group 2, hyper-reactors to the cold pressor test whose ages ranged from 19 to 59 years; Group 3, patients who had well-established hypertension whose ages ranged from 32 to 62 years; and Group 4, patients suspected of having pheochromocytoma, whose ages ranged from 39 to 59 years.

In the first three groups the blood pressure rose to a level somewhat less than the elevation obtained by the cold pressor test. Except for flushing of the face with subsequent headache, which was most intense in the patients with severest hypertension and pronounced tachycardia, no other symptoms were present. The results of the test were regarded as negative. In 1 instance, typical histamine cephalalgia was produced by this amount of histamine base.

When histamine base was given to 3 patients who had pheochromocytoma, the blood pressure rose approximately 100 mm. more than the elevation obtained by the cold pressor test. This elevation of blood pressure was accompanied by the characteristic symptoms of a typical spontaneous attack.

Although the number of cases in this series is small, the intravenous injection of small quantities of histamine base may be considered tentatively as a worth-while test in distinguishing the syndrome of pheochromocytoma from other clinical conditions.

#### REFERENCES

1. BEER, E., KING, F. H., and PRINZMETAL, M.: *Ann. Surg.*, **106**, 85, 1937.
2. BEST, C. H., and TAYLOR, N. B.: *The Physiological Basis of Medical Practice: A University of Toronto Text in Applied Physiology*, 3rd ed., Baltimore, Williams & Wilkins, p. 1157, 1943.
3. BRUNSCHWIG, A., and HUMPHREYS, E.: *J. Am. Med. Assn.*, **115**, 355, 1940.
4. HORTON, B. T., and ROTH, G. M.: *Proc. Staff Meet., Mayo Clin.*, **14**, 419, 1939.
5. HYMAN, A., and MENCHER, W. H.: *J. Urol.*, **49**, 755, 1943.
6. KVALE, W. F., ROTH, G. M., and CLAGETT, O. T.: *Surg. Clin. North America*, p. 922, 1944.
7. ROTH, G. M., and KVALE, W. F.: *Proc. Central Soc. Clin. Res.*, **17**, 18, 1944.

## A STUDY ON THE PREVENTION OF MUMPS ORCHITIS BY GAMMA GLOBULIN\*

BY SYDNEY S. GELLIS, CAPT., M.C., A.U.S.

AIMS C. MCGUINNESS, LT. COL., M.C., A.U.S.

AND

MICHAEL PETERS, CAPT. M.C., A.U.S.

ALTHOUGH the involvement of the salivary glands in mumps is seldom incapacitating, the orchitis which frequently complicates the disease in adults gives rise to considerable pain and discomfort, results in lengthy hospitalization, and causes much mental disturbance over the fear of subsequent sterility. For these reasons it appeared important to investigate the possibility of reducing the incidence of orchitis complicating outbreaks of mumps in the armed forces.

In the spring of 1944 an outbreak of the disease at Fort Benning, Georgia, presented the opportunity of determining the value of gamma globulin in the prevention of orchitis.

*Series 1.* Gamma globulin prepared from mumps convalescent serum was used in the initial series. The serum, collected from 395 patients at an army camp 1 to 3 months following recovery from mumps, was processed in the Department of Physical Chemistry of the Harvard Medical School through the courtesy of Dr. E. J. Cohn and Dr. J. L. Oncley:† 20 ml. of globulin were given intramuscularly to alternate patients admitted to the Station Hospital at Fort Benning with parotitis. Only those patients whose glandular swelling had been present 24 hours or less were admitted to the study. Patients who complained of testicular ache at the time of admission to the hospital were excluded. Physical examinations were performed daily on all patients and careful records were maintained. The patients were hospitalized for approximately 1 month in order to insure personal observation of any cases of orchitis which developed. In the event that globulin delayed but did not prevent the occurrence of orchitis a further check on the injected men was made 1 month after discharge from the hospital. The injected men and controls were confined to bed from the time of admission to the end of the 1st week of hospitalization but thereafter they were permitted to walk about the ward.

The results of this study are recorded in Table 1:

TABLE 1

		No. patients who developed orchitis	Incidence of orchitis (%)
No. of injected patients . . .	51	4	7.8
No. of controls . . . . .	51	14	27.4

\* This work was carried out under the direction of the Commission on Measles and Mumps of the Army Epidemiological Board, Preventive Medicine Service, Office of the Surgeon General, U. S. Army, 1818 H Street, N.W., Washington, 25, D. C.

† The preparation and testing of the globulin was carried out under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

Of the total patients with mumps studied (502), aside from those concerned with the investigation of the globulin, 25% developed orchitis subsequent to admission. Inclusion of patients with orchitis on admission raised the incidence of this complication to 32%.

*Series 2.* Because of the small supply of convalescent serum gamma globulin available, the above study was terminated and a similar experiment was conducted using gamma globulin from pools of normal human plasma. Enders<sup>1</sup> has shown that the complement fixing antibody for mumps antigen is concentrated approximately 20 times in this preparation of globulin. Since the titer of antibody is lower than that of gamma globulin obtained from convalescent serum a larger dose was administered to the men in this series. As in Series 1, alternate patients in the first 24 hours of the disease were given globulin. 50 ml. of globulin were administered, half being injected into each buttock. The results of this study are recorded in Table 2:

TABLE 2

	No. patients who developed orchitis	Incidence of orchitis (%)
No. of injected patients . . . 67	14	20.9
No. of controls . . . . . 67	18	26.8

Although these studies involve relatively small groups they suggest that convalescent serum gamma globulin is highly effective in the prevention of mumps orchitis, whereas gamma globulin from normal human plasma is of little value in this respect, nor in the latter group would there appear to be any attenuating effect.

**Discussion.** Hess<sup>2</sup> in 1915 was the first to employ human antibody, in the form of convalescent whole blood, in the prevention of mumps. Since then several studies have been conducted with mumps convalescent serum in the attempt to prevent the disease, modify its course, or lower the incidence of orchitis. The results of these studies are conflicting. It appears to be the present consensus of opinion that mumps convalescent serum will confer a temporary, brief, passive immunity which is of value in controlling outbreaks of the disease. However, the efficacy of convalescent serum in modifying the course of the disease or in prevention of orchitis is questionable. According to Gordon and Heeren,<sup>3</sup> "the administration of convalescent serum to patients with clinical parotitis in an effort to prevent other manifestations of the disease lacks proof of any worthwhile value." Iversen's series<sup>4</sup> showed a 20% incidence of orchitis in serum treated individuals as compared to 24% in those untreated. De Lavergne and Florentin<sup>5</sup> reported a reduction in orchitis from 24% in their control patients to 4% in their treated ones. In the series reported by Bailey and Haerem<sup>6</sup> 19.9% of the controls developed orchitis and 15.3% of the treated patients developed this complication. The amount of convalescent serum administered in the above studies ranged from 10 to 30 ml. per patient.

Variation in antibody titer of convalescent serum and differences in the dosage administered may account for conflicting results with con-

valescent serum. Bailey and Haerem found that the incidence of orchitis in men receiving serum from convalescent mumps orchitis patients was much lower than in those receiving serum drawn from patients whose disease had been uncomplicated by orchitis. They felt that this difference might be due to the higher antibody titer in the serum of men recovering from mumps orchitis.

The present series differ from those previously reported in the large quantity of serum administered. Since the gamma globulin preparation represents approximately a 20- or 25-fold concentration of human plasma, the initial series which was given 20 ml. of convalescent serum globulin received the equivalent of 400 ml. of convalescent serum or the equivalent (in antibody content) of 4000 ml. of normal pooled plasma. The second series, to which 50 ml. of globulin from normal human plasma were given, received the equivalent of 1250 ml. of normal plasma.

The mumps antibody in these preparations has been estimated by complement fixation tests carried out in Dr. J. F. Enders' laboratory, in the Department of Bacteriology, Harvard Medical School. The mumps antibody concentration, as estimated by the complement fixation test, has been referred to that in a standard preparation of gamma globulin from normal plasma, IIG66. The following table (Enders) gives the approximate results obtained for plasma and gamma globulin solutions from both normal and mumps convalescent donors:

TABLE 3 (ENDERS)

Source of donors	Ratio of mumps antibody (complement fixation test) to standard preparation IIG66	
	Plasma	Gamma globulin
Normal (American Red Cross blood donors)	0.04	1.0
Mumps convalescent . . . . .	0.5	10.0

Despite the large dose administered in the present studies it is evident that gamma globulin from pools of normal plasma in the doses employed is of no value in the prevention of mumps orchitis. However, the convalescent serum gamma globulin appears from the present small series to be highly effective and warrants further investigation.

**Summary.** 1. Alternate patients with mumps parotitis of 24 hours duration or less were given an intramuscular injection of 20 ml. of gamma globulin derived from mumps convalescent serum. The incidence of orchitis in the injected group was 7.8%, in the controls, 27.4%.

2. Alternate patients with mumps parotitis of 24 hours duration or less were given an intramuscular injection of 50 ml. of gamma globulin derived from pools of normal human plasma. 20.9% of the treated patients and 26.8% of the controls developed orchitis.

3. Gamma globulin derived from pools of normal human plasma is ineffective in the dosage employed in the present study in reducing the incidence of orchitis complicating mumps, whereas gamma globulin from mumps convalescent serum appears highly effective in this respect and warrants further investigation.

We wish to acknowledge the kind assistance of Maj. Marshall J. Coleman and Capt. Archie Y. Eagles.

## REFERENCES

1. ENDERS, J. F.: The Concentrations of Certain Antibodies in Globulin Fractions Derived From Human Blood Plasma, *J. Clin. Invest.*, **23**, 510, 1944.
2. HESS, A. F.: Protective Therapy for Mumps, *Am. J. Dis. Child.*, **10**, 99, 1915.
3. GORDON, J. E., and HEEREN, R. H.: The Epidemiology of Mumps, *Am. J. Med. Sci.*, **200**, 412, 1940.
4. IVERSEN, P.: Complications of Epidemic Parotitis and Experimental Treatment With Convalescent Serum, *Ugesk. f. læger*, **92**, 167, 1930.
5. DE LAVERGNE, V., and FLORENTIN, P.: Convalescent Serum in Prevention of Orchitis in Mumps, *Bull. Acad. de méd.*, **93**, 362, 1925.
6. BAILEY, W. H., and HAEREM, A. T.: Some Observations on the Efficacy of Convalescent Mumps Serum, *Mil. Surg.*, **90**, 134, 1942.

# PROGRESS OF MEDICAL SCIENCE THERAPEUTICS

UNDER THE CHARGE OF  
CARY EGGLESTON, M.D.

ASSOCIATE PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE  
AND

HARRY GOLD, M.D.

ASSOCIATE PROFESSOR OF PHARMACOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE,  
NEW YORK CITY

---

## THE PHARMACOLOGY AND THERAPEUTIC APPLICATIONS OF ANTI-THYROID COMPOUNDS

BY WALTER F. RIKER

AND

W. CLARKE WESCOE

(From the New York Hospital, and the Department of Medicine and Department  
of Pharmacology of Cornell University Medical College, New York City)

THE fact that certain substances possess anti-thyroid activity was brought to the attention of experimentalists in 1928 when Chesney, Clawson, and Webster reported that the prolonged feeding of cabbage to rabbits resulted in hyperplasia of the thyroid gland.<sup>21</sup> They tested practically all of the Brassicæ and found that these plants also effected an enlargement of the thyroid in their animals. Because these materials were known to contain nitrile derivatives, Marine and co-workers<sup>67</sup> tested the cyanides for possible goitrogenic activity; they chose the least toxic of the cyanides, acetonitrile, for their study. A striking thyroid hyperplasia resulted when this compound was injected into rabbits daily for 21 days. Certain aromatic nitriles shared this property but to a lesser degree. Since the cyanides were known to interfere with oxygen utilization, it was concluded that substances which depress oxygen consumption probably increase thyroid activity. Marine had previously postulated that when an increased demand is made upon the thyroid, goitre will result if the iodine supply is deficient. Accordingly, these authors demonstrated that the goitre resulting from the administration of acetonitrile could be prevented completely by iodine. As will be seen later, this fact serves as an important point of difference between the mode of action of the cyanides on the one hand and of the thioureas and related compounds on the other.

Following Marine's work on the chemical production of goitre, there were relatively few investigations until 1941 when a new impetus was supplied by the report of the MacKenzie and McCollum that rats fed sulfaguanidine for a period of weeks developed a marked thyroid hyperplasia.<sup>66</sup> Independently, Richter and Clisby made a similar observation



while studying the chronic toxicity of phenylthiourea in rats.<sup>55,56</sup> Meanwhile, Kennedy, who had been working on the goitrogenic property of Brassica seed, suggested that the active principle of this material might be a thiourea derivative. He therefore tested allyl thiourea and noted that its prolonged oral administration to rats resulted in extreme hypertrophy of the thyroid gland; in preliminary experiments with thiourea he obtained similar effects.<sup>54</sup> These observations<sup>54,56,55,56</sup> were then confirmed and extended by Astwood and co-workers.<sup>7</sup> The conclusion was reached that these substances act by interfering with the synthesis of thyroid hormone.

As a result of these investigations, Astwood instituted a study of the relative effectiveness of 106 compounds derived from thiourea or aniline as inhibitors of thyroid function in rats. He reported that certain derivatives of aniline, particularly the sulfonamides, were active in this regard. In the thiourea group certain derivatives were found more effective than thiourea itself; in decreasing order of activity these were: 2-thiouracil, 2-thiobarbituric acid, *s*-diethyl thiourea, and 5-benzal-2-thiohydantoin.<sup>1</sup>

Astwood was the first to apply these results to the treatment of human thyrotoxicosis.<sup>2</sup> The dramatic findings reported by him stimulated a large number of studies in animals and man to elucidate the mechanisms and to explore the therapeutic potentialities of these compounds.

**Effect on the Thyroid Mechanism.** Following the initial reports of thyroid hypertrophy in rats after the prolonged feeding of sulfonamides, phenylthiourea, and thioureas, the MacKenzies and Astwood described in detail the effects of these substances on the thyroid mechanism.<sup>7,63</sup> In the intact animal, the characteristics of thyroid hypofunction were manifest; these included a gradual reduction in the basal oxygen consumption, decreased food intake, and impairment of growth and development. This general picture also appeared in animals fed thiouracil.<sup>1</sup> When rats were given thiouracil from birth, retardation in growth and development occurred.<sup>50</sup> Animals fed these drugs manifested an increased tolerance to low oxygen tensions in accord with the lowered metabolism.<sup>43,44,59</sup>

At postmortem examination the thyroid glands were grossly enlarged and hyperemic. Histological examination revealed varying degrees of colloid loss, increased vascularity, and increase in the height of the acinar epithelium. In many follicles papillary projections of the epithelium protruded into the lumen with extensive desquamation of cells. In some instances the acini had disappeared and the extensive growth of follicle epithelium formed a contiguous cellular mass. At a time when the most severe hyperplasia existed, the cellular pattern in all glands studied remained orderly with no suggestion of neoplasia. To the present there have been no reports of malignant changes occurring either in animals or man as a result of the administration of these substances.

The overall picture observed was one of varying grades of hyperplasia of the gland paradoxically associated with indications of hypothyroidism in the intact animal. Upon withdrawal of the drugs, the evidences of hypothyroidism disappeared and the histologic changes regressed toward normal.

**Mechanism of Action.** The mechanism by which the anti-thyroid substances exert their effects has received considerable attention. The course of events in animals after the administration of these compounds was propounded initially by Astwood *et al.* and the MacKenzies. They concluded that the effects observed were due to an interference with the production of thyroid hormone.<sup>7,63</sup> This was based on the following facts: It was learned that the presence of the pituitary was essential for the production

of thyroid hyperplasia with these drugs. In hypophysectomized rats the administration of these agents had no effect on thyroid histology; regressive changes were noted in the thyroids of these animals just as in untreated hypophysectomized rats. An attempt to restore the normal situation in the hypophysectomized rat by the concurrent feeding of whole pituitary powder and anti-thyroid drug made possible only the maintenance of a normal histologic picture with little evidence of thyroid stimulation. It seems clear from this that these materials do not cause the hyperplasia by a direct action on the thyroid, but rather that it results from pituitary stimulation.

In view of the indications of an augmented pituitary drive, one might expect to demonstrate an increase in the thyrotropic activity of the blood and pituitary of treated rats. Gordon, Goldsmith, and Charipper were unable to show this in rats fed sulfadiazine and thiourea for a prolonged period. Indeed, the thyrotropic activity of the blood serum and pituitary from these animals was less than that of untreated controls. In contrast, thyroidectomized rats, after 6 months, possessed an increased quantity of thyrotropic activity in the blood and pituitary.<sup>41,46</sup> This does not necessarily contradict the concept of an increased thyrotropic activity in the drug treated rats, but rather indicates an increased utilization and resultant inactivation of thyrotropic hormone by an enlarging thyroid gland. Proof that thyrotropic hormone is capable of stimulating the thyroid gland of thiouracilized rats has been shown from a metabolic standpoint. The thyroids of such animals exhibited an increased oxygen utilization *in vitro*. This increased respiration could be augmented further by previous treatment of the animals with both thiouracil and thyrotropic hormone.<sup>53</sup> This is consistent with the anatomical finding of more severe hyperplasia of the thyroid in rats treated with both substances rather than with either alone. These results therefore are in harmony with the hypothesis that in animals treated with these anti-thyroid drugs, there is an increased thyrotropic activity on the part of the pituitary. This is not the result of a direct action on the pituitary, but may be looked upon as a reflex effect.

That the effects of these compounds can be completely circumvented by thyroxin was the next important point in the elucidation of the mechanism of action. It was learned that the feeding of sulfaguanidine to rats did not prevent the calorigenic action or toxic effects of administered thyroid substance. Furthermore, it developed that the goitrogenic property of any of these compounds could be abolished by exogenous thyroxin.<sup>1,7,27,63</sup> The metamorphosis of tadpoles induced by the injection of thyrotropic hormone could be inhibited by thiouracil, while that induced by thyroxin could not.<sup>51</sup> This principle has been utilized as the basis of an assay procedure for thyroid hormone in which the amount of thyroxin necessary to maintain or restore the normal thyroid weight of thiouracilized animals was determined.<sup>27,82</sup> These facts show that the hypothyroid state resulting from the administration of these agents is not produced by an inhibition of the action of thyroid hormone.

It has been seen from earlier work that the hyperplasia of the thyroid following cyanide administration could be prevented completely by the administration of iodine.<sup>67</sup> In contrast to this, the feeding of large supplements of iodine was without effect on the hyperplasia occurring after the administration of sulfonamides, thiourea, and thiouracil.<sup>17,63</sup> The administration of organic iodine in the form of di-iodotyrosine exhibited but slight antagonism toward thiouracil.<sup>27</sup> This substance, a precursor of

thyroxin, was approximately 4000 times less effective than the latter in preventing thyroid hyperplasia. Therefore, the mode of action of these goitrogens, unlike that of the cyanides, is not associated with an iodine deficiency. In this laboratory we observed that the administration of iodide to rats prior to a course of thiouracil retarded the enlargement of the thyroid.<sup>86a</sup> This is explained on the basis of previous storage of hormone as the result of iodine, so that reflex pituitary stimulation is delayed when hormone formation ceases. Applications of this principle have been observed clinically.

On the basis of the results described, it was concluded that these substances interfere with the synthesis of thyroid hormone in the thyroid gland. In response to the gradual loss of available hormone, the anterior pituitary is activated, and the subsequent elaboration of thyrotropin produces an ineffectual hyperplasia of the thyroid. The resultant effect on the intact animal is similar to that seen after surgical ablation.

The details of the mechanism by which the synthesis of thyroid hormone is prevented have not yet been explained fully. Because of the failure of inorganic iodine to circumvent the block in hormone synthesis the conversion *in vitro* of inorganic iodine to organically bound iodine was examined. Franklin and Chaikoff, utilizing surviving thyroid slices demonstrated that sulfanilamide inhibited the conversion of iodine to di-iodotyrosine and thyroxin.<sup>34</sup> Baumann, Metzger, and Marinc reported that in animals treated with thiouracil there was rapid loss of both thyroxin and non-thyroxin iodine from the thyroid.<sup>11</sup> Further, the administration of iodide and di-iodotyrosine had no effect on this; the excess iodine was excreted promptly in the urine. Thyroid iodine loss also resulted in animals treated with thiouracil in contrast to glands made hyperplastic by thyrotropic hormone.<sup>5,23</sup> These findings were confirmed by tracer studies with radioactive iodine in normal and thiourea fed rats. Analysis of the thyroids from the treated rats disclosed no appreciable concentration of radioactive iodine in any form. The glands from controls contained a considerable amount chiefly in organic combination.<sup>55</sup> The feeding of thiouracil to rats also interfered with the incorporation of injected radioactive iodine into di-iodotyrosine and thyroxin.<sup>37</sup> In these studies it was found when thiouracil was withdrawn from the diet, that the amount of radioactive iodine converted to thyroxin increased with time. Full recovery of the iodine concentrating capacity of the thyroid was evident 14 days after the withdrawal of thiouracil. A comparison of the effects of thiouracil and thiocyanate on the iodine concentrating capacity of the thyroid *in vivo* has been made. The concentration of labeled iodine in the glands of the thiouracil animals was well below that of the controls. However, in the case of the thiocyanate treated rats, the quantity of radioactive iodine in the thyroid was significantly greater than that of the controls.<sup>81</sup> This provides an illustration of the difference in the iodine metabolism of the thyroid as affected by a goitrogen inhibitable by iodine and by one that is not.

Certain quantitative aspects of the action of thiouracil in inhibiting the *in vivo* iodine uptake by the thyroid have been investigated with radioactive iodine. In the chick, this inhibition was found to be at a maximum 1 hour after the injection of thiouracil and to be lost gradually over 24 hours. The degree of inhibition produced by submaximal doses proved to be a linear function of the logarithm of the dose. In contrast to the rapid loss of the iodine concentrating capacity of the thyroid after injec-

tion of thiouracil anatomic changes were not in evidence for at least 5 days.<sup>57</sup>

With the use of radioactive iodine the similarity between the hyperplasia produced by thiouracil and thyrotropic hormone has been supported. It was first demonstrated that the anatomic changes in the chick thyroid occurring after thiouracil were indistinguishable from those seen after thyrotropic hormone. The similarity was further manifest from the functional standpoint in that the glands made hyperplastic by thiouracil acquired, after thiouracil was withdrawn, a capacity to collect radioactive iodine in amounts greater than controls and comparable to that collected by thyroids made hyperplastic with thyrotropic hormone.<sup>56</sup>

The disturbance in the iodine metabolism brought about by these compounds has also been investigated *in vitro*; reference has already been made to the initial step in this direction.<sup>34</sup> In an extension of this work it was learned that sulfonamides which inhibit the conversion *in vitro* of radioactive iodine to di-iodotyrosine and thyroxin had little effect on the iodine concentrating capacity of surviving thyroid slices.<sup>35,88</sup> Further studies have shown that thiourea, allylthiourea, thiouracil, p-aminobenzoic acid, and thiocyanate were all capable of depressing the conversion of radioactive iodine to di-iodotyrosine and thyroxin. With the exception of thiocyanate, these substances at high concentrations did not interfere with the uptake of iodine by the thyroid slices.<sup>36</sup> These results are essentially in accord with the *in vivo* studies on iodine utilization. It must be realized that the failure of the thyroid in the intact animal to concentrate iodine after the administration of these compounds is a result of numerous factors not present in the isolated tissue. The apparent failure of certain iodination reactions to take place probably represents a primary effect of these agents. From these data, the original assumption that these compounds prevent the normal synthesis of thyroid hormone is well supported.

Other possible points of attack on the thyroid mechanism have been explored. Gyorgy, *et al.* have suggested that these sulfhydryl compounds may exert their effects by reason of their ability to retard oxidations.<sup>47</sup> Pertinent to this, it has already been demonstrated that the cytochrome-cytochrome oxidase system is involved in the formation of di-iodotyrosine and thyroxin by the thyroid gland.<sup>26</sup> Dempsey detected the presence of cytochrome oxidase and peroxidase in the thyroid follicle cells by means of the nadi and benzidine reagents respectively. The addition of thiouracil to the reagents easily inhibited the peroxidase, whereas the cytochrome oxidase reaction was not affected. Since it is known that iodide must be oxidized to iodine before it can react with tyrosine, it would seem logical that the inhibition of peroxidase should favor this reaction by allowing for the accumulation of peroxide. The effect of thiouracil on the peroxidase and cytochrome oxidase activity of the thyroid has been confirmed.<sup>52</sup> In addition, it was found not to inhibit the action of xanthine oxidase or of triosephosphate dehydrogenase.<sup>52</sup> The only oxidative enzyme known to be inhibited easily by thiouracil is tyrosinase.<sup>76</sup> These results cast some doubt on the theory that oxidative mechanisms in the thyroid are interfered with by these substances. It is clear, however, that the evidence in this regard is meagre and will require further study.

**Absorption, Distribution, and Elimination.** Studies have been carried out on the absorption, fate, and elimination of thiourea and thiouracil. Thiouracil has been shown to be rapidly absorbed from the gastro-intestinal tract. This was determined by analysis of segments of the gastro-intestinal tract of rats after the oral administration of thiouracil. It was found that

more than 80 % of a single oral dose disappeared from the gastro-intestinal tract within 2 hours. In man the rapidity of absorption was demonstrated by following the concentration of thiouracil in the blood and urine after ingestion. The drug was present in the blood 15 to 30 minutes after doses of 0.1 to 0.2 Gm. by mouth given to a normal fasting man.<sup>101,102</sup> Thiouracil has also been shown to be absorbed quickly from the gastro-intestinal tract in man as determined by blood analysis and the rapidity with which it appeared in the urine after ingestion.<sup>16</sup>

Following the ingestion of a single oral dose of thiouracil by a normal fasting individual, the peak concentration in the blood was reached within 15 to 30 minutes. From this point there was a gradual decline in the blood level, with complete disappearance in 48 to 72 hours. The blood concentration could be maintained fairly well by the administration of frequent small doses.<sup>101,102</sup>

On reaching the blood, thiouracil has been found to enter the cellular elements. The concentration in the blood cells was 2 to 7 times greater than in the plasma. A further breakdown revealed that the total thiouracil content of the erythrocytes in a given specimen of blood was roughly twice that of the leukocytes. From a consideration of the relative proportion of red cells to white cells in a given specimen, it was obvious that the individual leukocyte contained much more drug than did the individual erythrocyte. These findings were confirmed by the *in vitro* incubation of blood cells with thiouracil. It was proved that the lymphocytes and granulocytes actively absorb thiouracil from a plasma solution; the red cells were less efficient in this regard.<sup>102</sup>

Thiouracil has been found to be distributed to all body fluids thus far examined. These included cerebrospinal fluid, edema fluid, pericardial fluid, chest fluid, ascitic fluid, urine, and milk. The concentration in the cerebrospinal fluid, edema fluid, and pericardial fluid was approximately that of the plasma. Chest and ascitic fluid contained a concentration equal to that of whole blood. The concentration of the drug in breast milk was about 3 times that of the whole blood.<sup>102</sup>

Thiourea disappeared from the blood even more rapidly than did thiouracil.<sup>16</sup> It appeared in the urine, cerebrospinal fluid, and breast milk. The concentration in the milk approximated that of the serum, whereas there was a delay in its appearance in the spinal fluid.<sup>20</sup> Because of its easy diffusibility, thiourea has been used to measure changes in total body water; the results agree closely with those obtained by metabolic calculation.<sup>25</sup> In experiments on dogs and man, thiourea was found to be distributed throughout a volume of fluid in excess of that ordinarily designated as total body water. These results can most likely be accounted for on the basis of destruction of the drug in the body. In view of this, it has proven unsatisfactory as an agent for measuring body water.<sup>20</sup>

The presence of thiouracil in body tissues was ascertained in man by the analysis of surgical and autopsy specimens. The drug was found in large quantities in the bone marrow, thyroid, ovaries, and pituitary. In general, the concentration in the bone marrow was greater than that in other tissues. It was shown to be present also in the adrenals, pancreas, kidneys, spleen, liver, testes, striated muscle, brain, heart, lungs and prostate. Certain alterations in the condition of the thyroid affect drug storage in the gland. The amount present in adenomatous portions of thyroid tissue was much more than that in relatively normal sections of the same gland.<sup>102</sup> Experiments on guinea pigs have shown that thyrotropic hormone when given in conjunction with thiouracil greatly decreased

the amount of drug stored in the thyroid, whereas the administration of potassium iodide with thiouracil greatly increased drug storage.<sup>105</sup>

Experiments were carried out on rats to investigate the possibility of thiouracil destruction in the body. In view of the rapidity with which it disappeared from the gastro-intestinal tract, attention was first directed to the action of gastric and intestinal contents on the drug. The incubation *in vitro* of thiouracil with the contents from different portions of the gastro-intestinal tract revealed a destruction of the drug by gastric, duodenal, and jejunal contents; material obtained from the ileum was not effective in this regard. That this may be partly accounted for by the action of certain intestinal flora was shown by incubation *in vitro* of thiouracil with bacteria. *Staphylococcus aureus* and beta hemolytic streptococcus destroyed 35 to 50% of the drug, respectively; *E. coli*, however, caused no destruction. Attempts have been made to determine the amount of drug destroyed by the gastro-intestinal tract.

The rate and amount of thiouracil destroyed by body tissue was determined on rats. Results were said to indicate a rapid initial destruction by the body.<sup>101</sup> The capacity of specific rat tissues to destroy thiouracil was tested by the incubation *in vitro* of surviving slices with thiouracil; those tissues studied included kidney, adrenal, pancreas, liver, pituitary, thyroid, and muscle. All were said to destroy the drug.<sup>102</sup> The quantitative data, however, are not conclusive due to certain unexplained inconsistencies.

The nature of the metabolism of thiouracil in the animal organism is as yet uncertain. Examination of the urine of dogs fed the drug has been reported to show positive qualitative tests for uracil and cytosine.<sup>69</sup> This needs to be confirmed. The effect of thiouracil on the excretion of sulfur in man has received attention. It was found that a decrease in ethereal and inorganic sulfur occurred. There was, however, an increased excretion of neutral sulfur. This was partly accounted for by thiouracil itself; the remainder could not be attributed to cysteine, cystine, thiourea, thiocyanate, phenylsulfate, urochrome, or melanin.<sup>101</sup> In rabbits and man, thiourea has been found to produce similar changes in sulfur excretion.<sup>15,101</sup>

Thiouracil is excreted mainly in the urine; none has been found in stools of animal or man. Subsequent to the ingestion of 0.1 to 0.2 Gm. of thiouracil by normal fasting man, a small amount appeared in the urine in 30 minutes. The maximal urinary excretion occurred during the second hour, and excretion progressively declined to minute amounts in 12 to 24 hours. Following an intravenous dose appreciable quantities were present in the urine within 30 minutes. However, the urinary excretion in this instance was said to persist longer than after oral dosage. The amount of thiouracil excreted in the urine varied with the size and frequency of the dose. However, the greater the daily dosage, the lower was the percentage of the total dose excreted.<sup>101,102</sup> Further studies on the distribution, fate, and elimination of thiouracil are necessary.

Thiourea, like thiouracil, has been demonstrated to be excreted chiefly *via* the urine; none appeared in the stool. In man about 75% of an oral dose of thiourea could be recovered from the urine. As previously indicated, this most likely represents a destruction of the drug by the body.<sup>20</sup> The renal clearance of thiourea and certain of its derivatives has been investigated and contrasted with simultaneous urea and creatinine clearances. The filtration and reabsorption of thiourea by the dog kidney approximates closely that of urea.<sup>73</sup>

Methods for the determination of thiouracil and thiourea in body fluids and tissues have been described.<sup>16,19,24,103</sup>

**Other Effects of Anti-thyroid Drugs.** A number of papers have appeared reporting the effects of these compounds on organs and tissues other than the thyroid. It was stated that in more than 700 microscopic sections made from essentially all of the body tissues from many series of rats, there were no alterations of note with the exception of those occurring in the thyroid gland.<sup>50</sup> Within a reasonable dosage range this is true. Those changes observed in other organs are in general those secondary to hypothyroidism.

The MacKenzies in their report on the effect of sulfonamides and thiourea as inhibitors of thyroid function, described changes in the histological appearance of the anterior pituitary similar to those occurring after thyroidectomy. These consisted of a basophilia with a loss of eosinophiles.<sup>63</sup> This finding has since been confirmed for sulfonamides, p-aminobenzoic acid, thiourea, and thiouracil.<sup>43,60,65</sup> The abnormal histologic picture reverts to normal upon cessation of treatment.<sup>65</sup> The weight of the rat pituitary gland per unit of body weight was not altered by the feeding of either thiourea or thiouracil.<sup>58,104</sup> As previously indicated the changes in the pituitary are a secondary effect.

Investigations have been carried out on the effect of thiouracil and thiourea upon trophic hormones, other than thyrotropin, elaborated by the anterior pituitary. It was found that these drugs did not inhibit either the adrenotropic or gonadotropic hormones. In fact, the activity of adrenotrope was augmented. In addition assay of the pituitary for gonadotrope revealed a greater hormone content in the glands of treated rats.<sup>58,104</sup> It would appear from this that the increased activity of the anterior pituitary following treatment with these drugs may not be limited entirely to the thyrotropic hormone.

The adrenal glands removed from rats treated with sulfonamides, thiourea, and thiouracil have been examined. These glands were reported to be smaller than those from normal animals.<sup>58,60,104</sup> This is in harmony with the findings in thyroidectomized animals. From a functional standpoint the adrenals removed from rats treated with thiouracil manifest a normal oxygen uptake *in vitro*.<sup>53</sup> In 16 human subjects studies were made of the various constituents of the blood and urine which to some extent are known to represent adrenal function. No alterations were discovered to indicate a disturbed function.<sup>98</sup>

In thyroidectomized animals the liver is known to be slightly decreased in size. This however, has not been observed in rats treated with anti-thyroid compounds.<sup>58,60</sup> Liver slices taken from thiouracilized rats possessed a normal metabolic rate.<sup>53</sup>

There has been experimental evidence of kidney changes following anti-thyroid compounds. Atrophic changes with thiourea have been described in rats, similar to those following thyroidectomy,<sup>60</sup> although no significant change in kidney size has been observed.<sup>58</sup> Hematuria with kidney damage occurs after toxic oral doses of thiouracil in normal and thyroidectomized rats.<sup>70</sup> We have also noted hematuria with crystalline deposits of the drug in the kidneys, ureters, and bladder after large doses of thiouracil in rats.<sup>93</sup>

The anti-thyroid agents apparently possess a direct toxic action giving rise to respiratory distress with pulmonary edema. Acutely toxic doses of phenylthiourea, thiourea, and thiouracil produced rapidly fatal pulmonary edema. No other tissues were edematous.<sup>64,70,86</sup>

Experimental evidence showed that thiourea produced changes in the

heart. The heart rate was slowed in rats after prolonged administration. Such animals showed slight atrophy of the heart similar to that seen after thyroidectomy.<sup>60</sup> The heart acquires a tolerance to epinephrine; in these experiments the threshold concentration of epinephrine in the heart muscle necessary to cause cardiac death in rats was determined and was found to be lower for animals pre-treated with thyroxin and higher for animals pre-treated with thiouracil than in the case of the normal.<sup>78</sup>

In accord with the above report, it is of note that thiourea has been shown to inhibit the epinephrine response of certain smooth muscle preparations. This was effected at concentrations that did not interfere with normal behavior of the preparation.<sup>38</sup>

The young of thiouracil treated mothers appeared normal at birth, but had hyperplastic thyroids; developmental retardation was evident by the tenth day. This was thought to result from a placental and mammary transmission of the drug.<sup>50</sup> Other experiments have confirmed and extended this conclusion.<sup>45</sup> Fetuses removed from thiouracil treated females at term contained a drug concentration one-half that of the mother. The amount of thiouracil in the placenta was slightly more than that of the mother.<sup>101</sup>

In view of the clinical experience with these drugs, perhaps the most important side action is that on the bone marrow. Feeding thiourea to rats produced a definite neutrophilic granulopenia which was preventable by the concurrent administration of solubilized liver extract. It was suggested that the active agent of the extract was probably folic acid.<sup>40</sup> A leucopenia and anemia has also been noted in rats fed thiouracil.<sup>104</sup> This effect must undoubtedly be related to the high concentration of thiouracil observed in the bone marrow of all animals treated. In this regard it is noteworthy that in studies on the distribution of radioactive sulfur in the rat, by far the highest concentrations were found in the bone marrow.<sup>89</sup>

Experiments on the effect of thiouracil on the respiration of bone marrow *in vitro* showed that high concentrations of the drug produce a small but significant inhibition. This was more pronounced in marrows made predominantly myeloid. Attempts to reverse this by the addition of pyridoxine or liver extract were unsuccessful.<sup>92</sup>

The serum and homogenized liver of rats treated with thiouracil possessed cholinesterase activities approximately twice those of control animals. The cholinesterase activity of the cerebral hemispheres from these rats was within normal limits.<sup>31</sup>

It was previously pointed out that malignant changes have not been observed in either animals or man treated with these drugs. However, benign and malignant tumors of the thyroid have been produced in rats by the combined administration of allylthiourea and a carcinogen, 2-acetylaminofluorene. Neither substance alone was capable of inducing thyroid neoplasia.<sup>14</sup> In a recent editorial the question has been raised as to the possibility of clinical cancer occurring during thiouracil treatment of older patients in whom some carcinogenic factor may be present.<sup>30</sup>

**Other Anti-thyroid Agents.** In 1943 Carter and co-workers described experiments which led to the conclusion that the basal metabolic rate of the rat is controlled by an interaction between thyroxin and an anti-thyroid substance identified as paraxanthine (1,7-dimethylxanthine).<sup>18</sup> The response was such that a daily dose of 20 micrograms orally produced a reduction of approximately 25% in the basal metabolic rate. When this dose was exceeded the metabolic rate rose toward normal and reached this level with double the dose. Above this dosage there was no further response.



Others have been unable to confirm the anti-thyroxin effect of paraxanthine by *in vitro* and *in vivo* experiments.<sup>42,96</sup>

Thiobarbital has been reported to be a more active goitrogen in rats; it was suggested that it is possibly less toxic.<sup>6</sup>

Tetramethyl thiourea has been shown in rats to have properties similar to other thiourcas.<sup>95</sup>

**Clinical Studies.** More than two years have elapsed since Astwood published a report on 6 clinical trials with anti-thyroid drugs.<sup>2</sup> Since then a voluminous clinical literature has accumulated and at the time of this writing reports have been made on more than 1000 cases. Many of these are of short term studies and are merely preliminary, but sufficient long range studies have been carried out to allow some evaluation of the drugs.

**Drugs Utilized.** In the clinical series thus far published these drugs have been used: thiourea,<sup>49,72,77,91</sup> thiouracil, thiobarbital,<sup>4</sup> 6-ethyl thiouracil,<sup>4</sup> allylthiourea,<sup>48</sup> tetramethyl thiourea,<sup>95</sup> di-ethyl thiourea,<sup>95</sup> and p-aminobenzoic acid.<sup>13</sup> Of these thiouracil has had the most extensive trial.

**Dosage.** There has been no standard method of dosage accepted and wide ranges of dose have been used in various clinics. All medication was given orally unless otherwise indicated. For the sake of clarity each drug will be considered individually.

**Thiouracil.** The greatest variations in dosage have been met with in the case of this drug. In early investigations daily dosages of 1 to 1.2 Gm. were not considered excessive,<sup>9,12,49,74,77</sup> and one clinic reports a daily dose of 2 Gm. in one case.<sup>8</sup> It was soon learned that beyond certain limits large doses were no more effective than smaller ones, and a lower scale of doses has been used generally in the last year. Various schedules of initial and maintenance therapy have been employed and of these 2 effective ones deserve special comment. One method<sup>28,84,94,100</sup> has been to give an initial daily dose of 0.6 Gm., to give 0.4 Gm. daily when the basal metabolic rate has fallen halfway to normal, and then to give 0.1 or 0.2 Gm. daily for maintenance as the individual case requires. The second method has been to give 0.6 Gm. daily initially, continuing thus until the basal metabolic rate has fallen within normal limits; then 0.1 or 0.2 Gm. daily are given for maintenance. The doses are divided and given usually as 0.1 Gm. 2, 4 or 6 times daily. Both methods have been equally effective in producing remissions. It would appear from the clinical data that the incidence of toxic reactions may be lower with the use of smaller amounts of the drug. This will be emphasized later.

**Thiourea.** Thiourea was the first drug used clinically and it was continued until thiouracil became more generally available. Comparatively larger amounts of thiourea were required. The common daily dose was 1 to 3 Gm.<sup>49,77</sup> These amounts were given in divided doses 2 or 3 times daily.

**Thiobarbital.** Originally thiobarbital was given in doses of 0.2 to 0.4 Gm. daily. This amount has since been reduced to 0.1 Gm. given in 1 or 2 doses.<sup>4</sup>

**6-ethyl Thiouracil.** The dose for this drug has not been effectively determined and amounts ranging from 0.02 to 0.1 Gm. daily have been tried in the 12 cases reported.<sup>4</sup>

**Allylthiourea.** This drug has had its only adequate trial in New Zealand. The dose given was 0.4 Gm. daily.<sup>48</sup>

**Tetramethylthiourea.** This compound has been given initially in doses of 0.6 Gm. daily; this was administered in 3 divided doses. The usual maintenance dose was 0.1 or 0.2 Gm. daily.<sup>95</sup>

**Diethyl Thiourea.** This substance was given similarly to tetramethylthiourea. Treatment was discontinued in all cases before maintenance therapy could be instituted.<sup>95</sup>

**p-aminobenzoic Acid.** This aniline derivative was given intramuscularly in daily doses of 1 to 1.5 Gm. for periods ranging from 3 to 9 months.<sup>13</sup>

Astwood reported that the effect of these compounds on the size of the thyroid in rats is a satisfactory guide to their potency in hyperthyroidism in man. Taking thiouracil as the standard with an assigned value of 1, the rat test gives thiourea a value of 0.13, and thiobarbital a value of 1.7. The observations in man show substantially similar relative values for these compounds.<sup>4</sup>

**Factors Influencing Therapeutic Response.** Nearly all patients with Graves' disease show partial or complete response to thiouracil. The incidence of failure is less than 2%, based on the failure to show significant response after the dosage in current use. It is noteworthy that even in these cases, one-half of the failures were reported in preliminary communications and in some in which the dose or period of trial was manifestly inadequate.

Patients who "escape" from iodine have responded readily to thiouracil.<sup>77,84</sup>

There is great individual variation in the period which elapses between the beginning of treatment and the clinical response. Reports have placed this latent period at from 1 week to 5 months. Pre-treatment with iodine may delay the response to thiouracil. This effect appears to be due to the storage of thyroxin resulting from iodine treatment, and in accordance with the supposed mechanism of thiouracil action, the more thyroxin available at the time, the greater the delay of thiouracil effects.

Patients with toxic nodular goitre also show a delay in the onset of thiouracil response and in these it is also presumed to be due to the higher concentration of thyroxin present in the goitre.<sup>3,4,8,71</sup>

**Duration of Therapeutic Response.** The ultimate outlook for the patient with Graves' disease under thiouracil therapy cannot be ascertained since the drug has been in use for a period of only 2 years. The indications are that in order to maintain the therapeutic remission it is necessary to continue the drug for a long time. In the more than 1000 cases already reported, approximately 10% continued satisfactorily after the drug was withdrawn. It is noteworthy that in one series of 48 patients in which a thyroid remission was induced by thiouracil therapy for 6 months or longer, the therapeutic effects continued in 77% of the cases when the drug was withdrawn.<sup>8</sup> There seems to be a relationship between the duration of therapy and the tendency to maintain a thyroid remission after the therapy is discontinued. Astwood has advised at least 6 months of treatment.<sup>4</sup> This is of necessity an empirical figure but there does not seem to be any method by which the optimum time can be determined; experience has proved that the promptness of response, the tendency to therapeutic myxedema, the severity of the thyrotoxicosis, the decrease in gland size, and the disappearance of a bruit are not reliable indications for cessation of therapy.<sup>3,8,71</sup> Relapses have been prompt and frequent in patients treated for periods shorter than 6 months. It is important, however, that all patients who relapse can be re-treated successfully with the drug.

A report of 6 cases of thyrotoxicosis treated with p-aminobenzoic acid has been published. The drug was given intramuscularly in large doses

for 3 to 9 months and produced a remission in each patient. These remissions were sustained 4 to 15 months after therapy was discontinued.<sup>13</sup> This work needs confirmation.

**Thyrotoxicosis With Complications.** Almost every clinical report has contained at least 1 thyrocardiac and experience has shown that cardiac complications are not a contraindication to thiouracil. Indeed there have been recorded 13 instances of auricular fibrillation and 1 instance of paroxysmal auricular flutter reverting to normal rhythm under thiouracil alone.<sup>3,8,12,28,49,68,84</sup>

The other most common complication was diabetes and 2 of the few failures reported have occurred in diabetic patients;<sup>8,84</sup> on the other hand 6 diabetics have been treated successfully for their thyrotoxicosis. Glycosuria disappeared in 2 other patients under treatment with thiouracil.<sup>28</sup>

Four acromegalics have been treated but the reports on them were contradictory.<sup>3,9</sup>

Of exceeding interest were 2 patients who were treated during pregnancy with thiouracil.<sup>29</sup> One was given the drug all during pregnancy until the last month when iodine was substituted; both mother and child were in excellent condition 5 months postpartum. The other was given thiouracil throughout the entire pregnancy; at delivery the child's thyroid was palpably enlarged but receded rapidly. There was no retardation of its growth or development. No mention of breast feeding was made; this would be of import since thiouracil is present in human milk.

There have been 3 other instances reported of thiouracil administered to pregnant women.<sup>68,87,98</sup> In each case the pregnancy and delivery were uncomplicated. No comments were made of any deleterious effects on the child. Apparently the drug may be given with safety in pregnancy.

**Effect on the Thyroid in Man.** The reactions of the thyroid to thiouracil as described in animals have, in the main, been confirmed in man. Although in animals when the gland changes size during thiouracil treatment there is always an enlargement, in humans the size of the gland may remain unchanged or it may increase or decrease. There are instances in which relatively large doses early in the course of the treatment caused increase in the size of the gland with symptoms of pressure and pain.<sup>4,49,83</sup> In other cases the gland decreased in size, especially after prolonged treatment.<sup>94,99</sup> In cases in which thiouracil produced no conspicuous changes in the gland, the administration of iodine reduced the size of the gland in much the same way as it does in cases without thiouracil.<sup>3</sup> In general it appears that changes in the size of the gland under thiouracil treatment are minimal, and frequently fall within the limits of error in measurement.

The histologic picture in man resembles that found in laboratory animals. Glands removed at operation subsequent to thiouracil therapy showed hyperplasia and increased vascularity. In 2 of 5 cases a statistically significant increase in the mean height of the acinar epithelium occurred after treatment. In the same series mention is made that involution and not hyperplasia was found in glands from patients treated with iodine previous to thiouracil therapy.<sup>80</sup>

Gland activity has been studied by means of blood hormonal iodine levels and by tracing radioactive iodine. It has been shown that the treated gland takes up much less iodine than does the normal, as is the case in the laboratory animal. Under treatment the level of circulating hormonal iodine falls toward normal.<sup>4,61,80,97,99</sup>

**Effect on Metabolism.** One of the most frequent laboratory procedures in clinical studies on thyrotoxicosis has been the determination of the basal metabolic rate. Study of the literature brings to light certain generalities

which can be made concerning the effect of these drugs on metabolic rate. Early papers showed that the fall in the basal metabolic rate following thiouracil treatment was directly comparable to that seen in the older series treated with iodine.<sup>3,80</sup> The fall appeared to be most precipitous in the first 2 weeks and then gradually became less rapid.<sup>3,94</sup> Unlike the results with iodine there was no tendency "to escape" during continued treatment. In general the higher the metabolic rate, the sharper the decline, although the precise reaction is not predictable. The rate at which the basal metabolic rate fell to normal was variable; in one series the range was from 4 to 108 days but 80 % of the patients reached normal in 10 to 40 days.<sup>8</sup> The basal metabolic rate resisted a fall below normal levels.<sup>49</sup>

Other metabolic functions have been studied. It has been stated that the first detectable effect of thiouracil is a fall in the circulating hormonal iodine.<sup>61</sup> Creatinuria was decreased during therapy; this was one of the earliest changes. The creatine tolerance was increased toward normal. In general the circulation time was increased. The earliest study on the metabolic effects of thiouracil was made by Sloan and Shorr.<sup>90</sup> This disclosed that the nitrogen, calcium, and phosphorus balances tended to become progressively more positive. The serum cholesterol level rose; it was noted that it often attained myxedematous levels before the basal metabolic rate gave evidence of myxedema. This was considered a reliable indication for decreasing the dose of the drug.<sup>8</sup>

**Effect on Symptoms.** It is difficult to tabulate chronologically the order of the disappearance of symptoms after beginning thiouracil therapy. There was agreement that the skin flush, tension, and irritability were the first to disappear and that the tachycardia was the last. The patient usually experienced subjective relief in advance of laboratory evidence of a response to the drug.<sup>3,8,28,49</sup>

**Effect on Exophthalmos.** For the most part thiouracil and other antithyroid drugs have no effect on the exophthalmos associated with thyrotoxicosis.<sup>4,28,49,90</sup> Apparent decrease in exophthalmos is brought about by a lessened lid spasm and by a gain in body weight during treatment.<sup>3,4,8,9,49</sup> Several cases of an increase in exophthalmos were reported by Barr and Shorr.<sup>8</sup> Combined therapy with thyroid extract or thyroxin has been said to cause improvement in some cases; in none of these latter cases was the action of thiouracil impeded.<sup>22,74,99</sup>

**Effect of Added Iodine.** We have already mentioned that pre-treatment with iodine may cause a delay in the response to thiouracil. Once thiouracil has acted, however, additional iodine elicits further response. Despite its inability to lead to the formation of thyroxin in a gland under the influence of thiouracil, it appears to reduce the vascularity and to cause persistent bruits to disappear; likewise it is capable of inducing histological involution of the gland.<sup>4,8,80</sup> These effects have prompted the use of iodine late in the thiouracil preparation of the patient for thyroidectomy.<sup>10</sup>

**Pre-operative Use.** Thyroidectomy has been carried out subsequent to thiouracil therapy in 2 types of cases. These were either patients who developed untoward reactions to the drug or patients in whom the drug was used to test its efficacy in pre-operative preparation. As a pre-operative measure thiouracil is advantageous because it can be used in cases which have become unresponsive to iodine.<sup>75</sup> Probably its most distinct advantage was that the metabolic state more closely approached the normal than with iodine; the patient became a better operative risk. Further, the problem of anesthesia and sedation was more satisfactorily managed.<sup>10</sup> The pre-operative treatment should be carried out until the basal metabolic rate has reached normal levels.

The disadvantages encountered in operation were: increased vascularity of the gland, occasional difficulty in controlling hemorrhage, and occasional difficulty in establishing cleavage planes, the latter particularly in patients who had had previous thyroidectomies.<sup>9,22,71,75</sup> The vascularity and bleeding were controlled to some extent by the addition of iodine in the latter days of thiouracil treatment.<sup>10</sup> The post-operative course of patients pre-treated with thiouracil has been uneventful; no instance of thyroid storm has occurred and only a few post-operative fevers have been reported.<sup>22,71,74,77,99</sup> On the whole, the smoother post-operative course makes thiouracil a distinct improvement over iodine.

**Toxic Reactions.** The major disadvantage in the use of anti-thyroid drugs has been the incidence of toxic reactions. For the most part these reactions are not serious and all save one are alleviated by withdrawal of the drug or reduction of the dose; the sole exception is agranulocytosis. At present there are reports of 5 deaths directly attributable to these drugs.

The toxic reactions to thiourea most usually encountered were nausea, vomiting, and halitosis. One case of granulopenia and thrombopenia was reported.<sup>72</sup> The reaction occurred 5 weeks after the onset of treatment and after 83 Gm. of the drug had been given. A study of the bone marrow showed a reduction of platelets and mature polymorphonuclear cells. The patient recovered when the drug was discontinued. Fever and maculopapular rash have also been reported.<sup>91</sup>

The toxic reactions to thiobarbital have consisted of fever, arthralgia, and myalgia which occurred in the second week of treatment and which lasted for 4 to 7 days even after the drug was withdrawn. Two other reactions have been described: 1 case of acute liver failure and 1 case of agranulocytosis which terminated fatally.<sup>4</sup>

The toxic reactions encountered thus far with tetramethylthiourea have been fever, rash, and urticaria.<sup>95</sup>

In the case of diethylthiourea all 4 patients treated developed headache, anxiety, palpitation, and slight dyspnea.<sup>95</sup> These are in all probability the result of circulatory disturbances characteristic of this class of compounds.<sup>32</sup>

The reactions to thiouracil have been numerous. Those which occurred with least frequency were: fever,<sup>8</sup> arthralgia, jaundice,<sup>33,63,90</sup> diarrhea,<sup>68</sup> lymphadenopathy,<sup>33,39,68,71</sup> edema of the legs,<sup>12,28,68</sup> urticaria,<sup>68</sup> conjunctivitis,<sup>8,12</sup> low carbon dioxide combining power,<sup>22</sup> oral infections,<sup>71</sup> nausea,<sup>8</sup> crystalluria,<sup>74</sup> and hematuria.<sup>8,74</sup> These reactions were controlled when the drug was withdrawn or the dosage was reduced. Crystalluria was successfully treated in one series by the concurrent administration of sodium bicarbonate.<sup>74</sup> This point needs confirmation for D. R. Gilligan (unpublished data) reports that there is virtually no difference in the solubility of thiouracil in the urine over the physiological range of pH. Not all of these reactions can be traced specifically to the drug; the fever and conjunctivitis could be definitely attributed to the drug since both reactions recurred promptly following a test dose.

The serious reactions to thiouracil have involved the blood and blood-forming organs. Neutropenia has been reported in at least 35 cases; this could be relieved by withdrawal or reduction of the drug. In other cases the neutropenia did not persist even when the drug was continued in the same dose.

The fatal reactions to thiouracil have all been caused by agranulocytosis. At the time of this writing 3 such cases have been reported. These occurred from 6 weeks to 1 year after treatment was begun. Bone marrow studies

have been performed in several cases; all showed a deficiency of the myeloid elements and a maturation arrest in the myeloid series.<sup>62</sup> It is noteworthy in this respect that 1 case of agranulocytosis was foreshadowed by the appearance of immature forms of the myeloid series in the peripheral blood.<sup>49</sup> With improvement the bone marrow precedes the peripheral blood to normalcy. The most important factors in the treatment of agranulocytosis have been the prompt withdrawal of the drug and the control of infection with penicillin.<sup>8</sup> The liver extract advocated on the basis of laboratory experiment has been used in treatment; its value is still uncertain. Pyridoxine hydrochloride intravenously in large doses has been advocated for the treatment of agranulocytosis.<sup>17</sup>

The toxic reactions appeared to be a manifestation of acquired drug sensitization. This was borne out by the fact that subsequent small doses brought about a return of toxic symptoms.

**Treatment of Angina Pectoris.** A report has been published concerning the effect of thiouracil on angina pectoris.<sup>79</sup> Ten patients were included in the series. The daily dose of the drug varied from 0.4 to 1.2 Gm. Under treatment 8 of the 10 patients were relieved of pain; 4 of them became entirely symptom free. The therapeutic effect was correlated with the fall of the basal metabolic rate to subnormal levels. This report appears to us to be significant in light of the fact that thiouracil increases the tolerance of the rat heart to epinephrine.

In closing, it may be noted that the compounds which have been discussed have proved not only of great value in the treatment of Graves' disease, but have provided a new tool for the investigation of the physiology of the thyroid gland.

#### REFERENCES

- (1.) Astwood, E. B.: *J. Pharm. and Exp. Ther.*, 78, 79, 1943. (2.) Astwood, E. B.: *J. Am. Med. Assn.*, 122, 78, 1943. (3.) Astwood, E. B.: *J. Clin. Endocrinol.*, 4, 229, 1944. (4.) Astwood, E. B.: *Harvey Lectures*, 1945. In press. (5.) Astwood, E. B., and Bissell, A.: *Endocrinology*, 34, 282, 1944. (6.) Astwood, E. B., Bissell, A., and Hughes, A. M.: *Endocrinology*, 36, 72, 1945. (7.) Astwood, E. B., Sullivan, J., Bissell, A., and Tyslowitz, R.: *Endocrinology*, 32, 210, 1943. (8.) Barr, D. P., and Shorr, E.: *Ann. Int. Med.* In press. 1945. (9.) Bartels, E. L.: *J. Am. Med. Assn.*, 125, 24, 1944. (10.) Bartels, E. L.: *Ann. Int. Med.*, 22, 365, 1945. (11.) Baumann, E. J., Metzger, N., and Marine, D.: *Endocrinology*, 34, 44, 1944. (12.) Beardwood, J. T., and Levinson, D. C.: *Clinics*, 3, 672, 1944. (13.) Berman, L.: *Proc. Soc. Exp. Biol. and Med.*, 59, 70, 1945. (14.) Bielschowsky, F.: *Brit. J. Exp. Path.*, 25, 90, 1945. (15.) Blood, F. R., and Lewis, H. B.: *J. Biol. Chem.*, 139, 413, 1941. (16.) Campbell, D., Landgrebe, F. W., and Morgan, T. N.: *Lancet*, 1, 630, 1944. (17.) Cantor, M. M., and Scott, J. W.: *Science*, 100, 545, 1944. (18.) Carter, G. S., Mann, F. G., Harley-Mason, J., and Jenkins, G. N.: *Nature*, 151, 728, 1943. (19.) Chesley, L. C.: *J. Biol. Chem.*, 152, 207, 1944. (20.) Chesley, L. C.: *J. Clin. Invest.*, 23, 856, 1944. (21.) Chesney, A. M., Clawson, T. A., and Webster, B.: *Bull. Johns Hopkins Hosp.*, 43, 261, 1928. (22.) Clute, H. M., and Williams, R. H.: *Ann. Surg.*, 120, 504, 1944. (23.) Couceiro, A., Vieira, L., and De Moraes, J.: *Brasil. Biol.*, 4, 173, 1944. (24.) Danowski, T. S.: *J. Biol. Chem.*, 152, 201, 1944. (25.) Danowski, T. S.: *J. Biol. Chem.*, 152, 207, 1944. (26.) Dempsey, E. W.: *Endocrinology*, 34, 27, 1944. (27.) Dempsey, E. W., and Astwood, E. B.: *Endocrinology*, 32, 509, 1943. (28.) Dunlop, D. M.: *Edinburgh Med. J.*, 52, 30, 1945. (29.) Eaton, J. C.: *Lancet*, 1, 171, 1945. (30.) Editorial: *J. Am. Med. Assn.*, 127, 278, 1945. (31.) Ellis, S., and Root, M. A.: *Fed. Proc.*, 3, No. 1, 1944. (32.) Fastier, F. N., and Smirk, F. H.: *J. Physiol.*, 101, 379, 1943. (33.) Ferber, M. I., Spain, D. M., and Cathcart, R. T.: *J. Am. Med. Assn.*, 127, 646, 1945. (34.) Franklin, A. L., and Chaikoff, I. L.: *J. Biol. Chem.*, 148, 719, 1943. (35.) Franklin, A. L., and Chaikoff, I. L.: *J. Biol. Chem.*, 152, 295, 1944. (36.) Franklin, A. L., Chaikoff, I. L., and Lerner, S. R.: *J. Biol. Chem.*, 153, 151, 1944. (37.) Franklin, A. L., Lerner, S. R., and Chaikoff, I. L.: *Endocrinology*, 34, 265, 1944. (38.) Friedenwald, J. S., and Buschke, W.: *Am. J. Physiol.*, 140, 367, 1944.

- (39.) Gabrilove, J. L., and Kert, M. J.: *J. Am. Med. Assn.*, 124, 504, 1944. (40.) Goldsmith, E. D., Gordon, A. S., Finkelstein, G., and Charipper, H. A.: *J. Am. Med. Assn.*, 125, 847, 1944. (41.) Gordon, A. S., Charipper, H. A., and Goldsmith, E. D.: *Anat. Rec.*, 87, 445, 1943. (42.) Gordon, A. S., Charipper, H. A., and Goldsmith, E. D.: *Anat. Rec.*, 89, 566, 1944. (43.) Gordon, A. S., Goldsmith, E. D., and Charipper, H. A.: *Anat. Rec.*, 88, 433, 1944. (44.) Gordon, A. S., Goldsmith, E. D., and Charipper, H. A.: *Science*, 99, 104, 1944. (45.) Gordon, A. S., Goldsmith, E. D., and Charipper, H. A.: *Am. J. Obst. and Gynec.*, 49, 197, 1945. (46.) Gordon, A. S., Goldsmith, E. D., and Charipper, H. A.: *Endocrinology*, 36, 53, 1945. (47.) Gyorgy, P., Stiller, E. T., and Williamson, M. B.: *Science*, 98, 518, 1943.
- (48.) Hercus, C. E., and Purves, H. D.: *New Zealand Med. J.*, 43, 213, 1944. (49.) Himsworth, H. P.: *Proc. Roy. Soc. Med.*, 37, 693, 1944. (50.) Hughes, A. M.: *Endocrinology*, 34, 69, 1944. (51.) Hughes, A. M., and Astwood, E. B.: *Endocrinology*, 34, 138, 1944.
- (52.) Jandorf, B. J.: Unpublished data, quoted by Williams, R. H., *Arch. Int. Med.*, 74, 479, 1944. (53.) Jandorf, B. J., and Williams, R. H.: *Am. J. Physiol.*, 141, 91, 1944.
- (54.) Kennedy, T. H.: *Nature*, 150, 233, 1942. (55.) Keston, A. S., Goldsmith, E. D.: Gordon, A. S., and Charipper, H. A.: *J. Biol. Chem.*, 152, 241, 1944.
- (56.) Larson, R., Keating, R., Peacock, W., and Rawson, R.: *Endocrinology*, 36, 149, 1945. (57.) Larson, R., Keating, R., Peacock, W., and Rawson, R.: *Endocrinology*, 36, 160, 1945. (58.) Leatham, J. H.: *Endocrinology*, 36, 98, 1945. (59.) Leblond, C. P.: *Proc. Soc. Exp. Biol. and Med.*, 55, 114, 1944. (60.) Leblond, C. P., and Hoff, H. E.: *Endocrinology*, 35, 229, 1944. (61.) Lowenstein, B. E., Bruger, M., Hinton, W. J., and Lough, W. G.: *J. Clin. Endocrinol.*, 5, 181, 1945. (62.) Lozinski, E., and Siminovich, J.: *Canadian Med. Assn. J.*, 51, 422, 1944.
- (63.) MacKenzie, C. G., and MacKenzie, J. B.: *Endocrinology*, 32, 185, 1943. (64.) MacKenzie, C. G., and MacKenzie, J. B.: *Proc. Soc. Exp. Biol. and Med.*, 54, 34, 1943. (65.) MacKenzie, C. G., and MacKenzie, J. B.: *Bull. Johns Hopkins Hosp.*, 74, 85, 1944. (66.) MacKenzie, J. B., MacKenzie, C. G., and McCollum, E. V.: *Science*, 94, 518, 1941. (67.) Marine, D., Baumann, E. J., Spence, A. W., and Cipra, A.: *Proc. Soc. Exp. Biol. and Med.*, 29, 772, 1932. (68.) McGavack, T. H., Gerl, A. J., Vogel, M., and Schwimmer, D.: *J. Clin. Endocrinol.*, 4, 249, 1944. (69.) Mendel, L. B., and Myers, V. C.: *Am. J. Physiol.*, 26, 77, 1910. (70.) Meyer, A. E., Collins, M. B., and Marine, D.: *Proc. Soc. Exp. Biol. and Med.*, 55, 221, 1944. (71.) Moore, F. D., Sweeny, D. N., Jr., Cope, O., Rawson, R. W., and Means, J. H.: *Ann. Surg.*, 120, 152, 1944.
- (72.) Newcomb, P. B., and Deane, E. W.: *Lancet*, 1, 179, 1944. (73.) Nichols, H. J., and Herrin, R. C.: *Am. J. Physiol.*, 135, 113, 1941.
- (74.) Palmer, M. J.: *Ann. Int. Med.*, 22, 335, 1945. (75.) Paschkis, K. E.: *Med. Clin. North America*, 28, 1362, 1944. (76.) Paschkis, K. E., Cantarow, A., Hart, W. M., and Rakoff, A. E.: *Proc. Soc. Exp. Biol. and Med.*, 57, 37, 1944. (77.) Paschkis, K. E., Cantarow, A., Rakoff, A. E., Walkling, A. A., and Tourish, W. J.: *J. Clin. Endocrinol.*, 4, 179, 1944.
- (78.) Raab, W.: *J. Pharm. and Exp. Ther.*, 82, 330, 1944. (79.) Raab, W.: *J. Am. Med. Assn.*, 128, 249, 1945. (80.) Rawson, R. W., Evans, R. D., Means, J. H., Peacock, W. C., Lerman, J., and Cortell, R.: *J. Clin. Endocrinol.*, 4, 1, 1944. (81.) Rawson, R. W., Tannheimer, J. F., and Peacock, W.: *Endocrinology*, 34, 245, 1944. (82.) Reineke, E. P., Mixner, J. P., and Turner, C. W.: *Endocrinology*, 36, 64, 1945. (83.) Reveno, W. S.: *J. Am. Med. Assn.*, 126, 153, 1944. (84.) Reveno, W. S.: *J. Am. Med. Assn.*, 128, 419, 1945. (85.) Richter, C. P., and Clisby, K. H.: *Proc. Soc. Exp. Biol. and Med.*, 48, 684, 1941. (86.) Richter, C. P., and Clisby, K. H.: *Arch. Path.*, 33, 46, 1942. (86a.) Riker, W. F., and Shorr, E.: Unpublished data. (87.) Rose, E., and McConnell, J.: *Am. J. Med. Sci.*, 208, 561, 1944.
- (88.) Schachner, H., Franklin, A. L., and Chaikoff, I. L.: *Endocrinology*, 34, 159, 1944. (89.) Singher, H. O., and Marinelli, L.: *Science*, 101, 414, 1945. (90.) Sloan, M. H., and Shorr, E.: *Science*, 99, 305, 1944. (91.) St. Johnston, C. R.: *Lancet*, 2, 42, 1944.
- (92.) Warren, C. O.: *Science*, 102, 175, 1945. (93.) Wescoe, W. C., and Riker, W. F.: Unpublished data. (94.) Williams, R. H.: *Arch. Int. Med.*, 74, 479, 1944. (95.) Williams, R. H.: *J. Clin. Endocrinol.*, 5, 210, 1945. (96.) Williams, R. H.: *J. Clin. Endocrinol.*, 5, 217, 1945. (97.) Williams, R. H., and Bissell, G. W.: *New England J. Med.*, 229, 97, 1943. (98.) Williams, R. H., Bissell, G. W., Jandorf, B. J., and Peters, J. B.: *J. Clin. Endocrinol.*, 4, 58, 1944. (99.) Williams, R. H., and Clute, H. M.: *New England J. Med.*, 230, 657, 1944. (100.) Williams, R. H., and Clute, H. M.: *J. Am. Med. Assn.*, 128, 65, 1945. (101.) Williams, R. H., and Kay, G. A.: *J. Clin. Endocrinol.*, 4, 385, 1944. (102.) Williams, R. H., Kay, G. A., and Jandorf, B. J.: *J. Clin. Invest.*, 23, 613, 1944. (103.) Williams, R. H., Jandorf, B. J., and Kay, G. A.: *J. Lab. and Clin. Med.*, 29, 329, 1944. (104.) Williams, R. H., Weinglass, A. R., Bissell, G. W., and Peters, J. B.: *Endocrinology*, 34, 317, 1944. (105.) Williams, R. H., Weinglass, A. R., and Kay, G. A.: *Am. J. Med. Sci.*, 207, 701, 1944.

## RADIOLOGY

UNDER THE CHARGE OF

HARRY M. WEBER, M.D. AND DAVID G. PUGH, M.D.

SECTION ON ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINNESOTA

## FIBROCYSTIC DISEASE OF THE PANCREAS

BY DAVID G. PUGH, M.D.

IN 1888 Gee described a condition encountered among infants and children which he called "celiac disease." For many years this condition was regarded as a disease entity but gradually it became apparent to various investigators that it was in reality a syndrome which could be produced by more than one disease. This syndrome consists of large pale offensive fatty stools, abdominal distention, anorexia, wasting, stunting of growth and symptoms of deficiency disease.<sup>23</sup> Owing to the type of bulky fatty stools that are usually seen, it is often called "steatorrhea," a term which has become almost synonymous with the term "celiac syndrome." In many cases the symptoms are produced without any clinical or postmortem evidence of pancreatic disease; in such cases the disease is classified as idiopathic steatorrhea or true celiac disease. As the result of many investigations, which are well described by Rauch, Litvak and Steiner,<sup>23</sup> it became obvious that in some cases disease of the pancreas with pancreatic insufficiency was present. These cases have been designated under various terms, such as "pancreatitis, pancreatic disease, atrophy of the pancreas, congenital pancreatic steatorrhea, celiac disease, congenital cystic fibromatosis of the pancreas, agenesis of the exocrine portion of the pancreas, congenital pancreatic disease, cirrhosis of the pancreas and congenital familial steatorrhea" (Wolman).<sup>26</sup> Since the pathologic changes in the pancreas are consistently similar in these cases, it is suitable to designate the condition as "fibrocystic disease of the pancreas" and avoid use of the synonyms.

Most of those who have studied pancreatic insufficiency with steatorrhea due to fibrocystic disease of the pancreas have been impressed by the constant association of chronic respiratory infection. In the past fibrocystic disease of the pancreas has been diagnosed most frequently at necropsy; recently, however, the diagnosis has been made before death in an increasing percentage of cases. If physicians were stimulated to suspect the condition more frequently, the diagnosis could be made with accuracy in many instances. At times this stimulus may be provided by the roentgenologist.

The pathologic picture of fibrocystic disease of the pancreas presented at necropsy is usually typical.<sup>1,9,12,14,23</sup> Few changes can be recognized grossly. There may be infiltration with fat or increased fibrous connective tissue between the lobules. The lobules may be rounded and uneven in size. Occasionally a grating sound may be produced as the knife passes through calcified concretions. The gland may appear firmer than normal and contain tiny opaque grayish yellow nodules. The pancreatic duct is patent in most cases. The histologic appearance may vary considerably, depending on the stage of development of the disease, though certain constant findings are seen in most cases. Dilated ducts and acini contain varying amounts of coagulated secretion. The cells of the epithelial lining



are flattened and, rarely, may be squamous in type. The secreted material occasionally has a laminated appearance and is usually acidophilic. The intra-acinar material stains like mucus and occasionally like fibrin. The acinar parenchyma is atrophied and the interacinar and interlobular connective tissue is increased and may be infiltrated with lymphocytes or mononuclear cells. The islands of Langerhans are usually normal in size and number, although slight but definite abnormality of these has been seen.

In association with the pancreatic changes pulmonary lesions are present almost invariably at the time of death.<sup>1,9,14,23</sup> Grossly these consist of suppurative bronchitis and bronchiectasis with patches of bronchopneumonia and abscesses. The bronchi usually are filled with mucopurulent exudate that is unusually thick and tenacious. Emphysema and atelectasis, usually in combination, are common findings. Thickening of the bronchiolar walls, replacement fibrosis in those portions of the lungs repaired after staphylococcal destruction and diffuse bilateral acute and chronic bronchopneumonia characterize the later stages of the disease. *Staphylococcus aureus* is present in most cases.

The pathogenesis of fibrocystic disease of the pancreas is not definitely known. Many early investigators regarded it as a congenital deformity which consists of stenosis or atresia of the pancreatic ducts. However, this has been found but rarely. The presence of this condition in the newborn and its early manifestations in infants, to be sure, does suggest congenital origin. A familial tendency has been observed by many who have studied the disease and this is indicated in many of the synonyms that have been used to describe this condition. In this regard, Daniel<sup>7</sup> said, "It must be stated that although the syndrome appears to be familial, often the affected child is the only infant in a large family who has or has had the disease." The congenital nature of the disease also is suggested by the frequency with which other congenital anomalies are found. Harper<sup>12</sup> said the disease was probably congenital. Rauch<sup>23</sup> and his associates thought that the lesions of both the pancreas and the lungs were due to congenital anomalies. They said that there appeared to be a congenital constriction of the pancreatic ducts and of the bronchial passages which might be explained by the embryologic development since the anlagen of the lungs and pancreas develop from a common endodermal tube. Congenital anomaly of the bronchial tree causes it to be more susceptible to infection and in this way they explained the pulmonary infection in this disease.

Patients who have this disease may have vitamin A deficiency. Some observers have suggested that this deficiency may result in obstruction of the pancreatic ducts by masses of desquamated epithelial cells—a concept that is not generally accepted. Parmelee<sup>22</sup> and later Andersen,<sup>1</sup> however, have suggested that the pulmonary infection may be secondary to changes in the bronchial epithelium resulting from vitamin A deficiency. Most observers doubt that vitamin A deficiency is of primary etiologic importance but recognize that it may become a complication.

It is frequently stated that the respiratory infection is probably only the result of lowered resistance. However, in many instances pulmonary involvement is marked before there is much evidence of malnutrition.

Blackfan and Wolbach<sup>6</sup> in 1933 suggested that the lesions of the pancreas might be due to thickening of acinar secretion; this inspissated material might cause obstruction with resulting hypofunction of the secretory mechanism. Farber<sup>8,9</sup> also advanced the theory that the pan-

creatic secretion is abnormal in fibrocystic disease of the pancreas, and that this causes intrinsic obstruction of the acini and small ducts, finally producing dilatation and obstruction in the larger ducts. He also found inspissation of secretion and dilatation of similar character in the glands of the trachea, bronchi, esophagus, duodenum, gallbladder and intestinal tract, the inspissation of bile perhaps being sufficient to cause intrahepatic biliary obstruction. He suggested that a generalized disorder of secretory mechanism must be present. This involves many glandular structures but exerts its greatest effect on the pancreas. This concept needs further confirmation.

Baggenstoss<sup>2</sup> and Kennedy<sup>3</sup> reported that in their cases the bronchi and their glands usually contained an exudate more purulent than mucoid. Occasionally the bronchial glands were distended with mucus. The only evidence of abnormal glandular secretion, except of these structures and the pancreas, was dilatation and distention of the glands of the duodenum.

Meconium ileus which is grouped with fibrocystic disease of the pancreas was described by Landsteiner<sup>16</sup> in 1905. The term is used to describe an intestinal obstruction in the newborn caused by inability of the intestines to propel through the lumen a thick, mucilaginous meconium, the altered physical state of which is explained by the failure of pancreatic enzymes, particularly trypsin, to act on it during intra-uterine life.<sup>8</sup> Rupture of the intestines and meconium peritonitis may occur. As a rule typical lesions are found in the pancreas at necropsy. There is pancreatic fibrosis with obstruction to the outflow of secretions. This obstruction has been proved in some cases to be due to congenital atresia or stenosis of the main pancreatic ducts. In other instances obstruction is not so obvious and the appearance is suggestive of the changes found in the pancreas of infants who have died of fibrocystic disease of the pancreas. Lesser degrees of intestinal obstruction may be produced by inspissated meconium resulting from stenosis of the ileocecal valve without pancreatic achylia. The condition has been reported as resulting from obstruction to the flow of bile into the intestines without any lesion of the pancreas. Respiratory infection does not occur in these patients, probably because they die so soon after birth. Hurwitt and Arnheim reported the cases of 2 infants who survived for some time after surgical intervention had relieved the intestinal obstruction. Both of these patients died as the result of respiratory infection. Meconium ileus has been reviewed recently by Hurwitt and Arnheim<sup>13</sup> and Kaufmann and Chamberlin.<sup>15</sup>

The current interest in fibrocystic disease of the pancreas is based largely on the independent investigations of the subject by Andersen<sup>1</sup> and Harper<sup>12</sup> in 1938 and Ranch, Litvak and Steiner<sup>23</sup> in 1939. Aided by observations made by earlier investigators supplemented with astute personal observations, these investigators have offered a lucid and coherent concept of fibrocystic disease of the pancreas as a disease entity. Farber<sup>8,9</sup> has contributed much to complete the picture.

Andersen<sup>1</sup> divided the cases of fibrocystic disease of the pancreas into 3 groups: (1) those in which death occurred in the neonatal period; there was intestinal obstruction due to meconium ileus; (2) those in which death occurred between the neonatal period and 6 months of age; the outstanding symptom in these cases was chronic respiratory infection but also there was failure to gain weight and, in some instances, other mild evidences of celiac syndrome; (3) those in which death occurred after the sixth month of age; chronic respiratory infection was present and in most instances the celiac syndrome was obvious.

Not much need be said with regard to patients who have meconium ileus. The outstanding symptoms are those of intestinal obstruction, and death comes rapidly. Neuhauser<sup>21</sup> reported having made the diagnosis of meconium ileus before death by means of roentgenologic methods; this topic will be mentioned later.

The second group described by Andersen is the largest, according to Farber, and includes the cases most difficult to recognize. The symptoms are predominantly those of chronic respiratory infection. Cough which usually is dry and brassy to begin with will persist, perhaps for weeks, and become productive. It frequently simulates the cough of pertussis. Gastro-intestinal symptoms may be moderate or absent. The patient's failure to gain weight may be falsely attributed to the chronic respiratory infection. Steatorrhea may be present but frequently is not obvious grossly and may be overlooked. Since the celiac syndrome often is not obvious, the true nature of the disability frequently escapes recognition until necropsy.

The third group described by Andersen is smaller than the second and usually offers less difficulty in diagnosis. As a rule the celiac syndrome is obvious and this with the associated chronic respiratory infection should suggest fibrocystic disease of the pancreas. The longer the patient survives the more likely that the typical celiac syndrome may be seen.

Fibrocystic disease of the pancreas must be distinguished from idiopathic steatorrhea. As many observers have noted, fibrocystic disease of the pancreas becomes apparent earlier in life. Prolonged chronic respiratory infection is an outstanding feature of this condition, whereas in idiopathic steatorrhea pulmonary infections are found only as an intercurrent infection or a terminal affair. Death in idiopathic steatorrhea is the result of exacerbation of the diarrhea as a rule. Patients who have idiopathic steatorrhea live longer than those who have pancreatic disease. The familial tendency is not found in idiopathic steatorrhea.

If fibrocystic disease of the pancreas is present, the diagnosis can be substantiated by estimating the pancreatic enzymes of the duodenal contents. Their absence or marked diminution (especially trypsin) is almost pathognomonic of the fibrocystic disease when it occurs in patients of this age who have the symptoms described. The fat content of the stools is an aid to diagnosis but this can be deceiving. It is true that in these cases the stools are often grossly fatty but at times this is not so obvious. In Andersen's second group it has been found that steatorrhea may be mild and may not be recognized. Also it must be kept in mind, when analyzing stools for fat, that the fat content of stool specimens of normal infants and children varies from 10 to 80% of dried feces.<sup>8</sup> The ratio of neutral fat to hydrolyzed fat does not serve to distinguish fibrocystic disease from idiopathic steatorrhea, as in the former intestinal lipase is still present.<sup>1,8</sup> Other laboratory tests are of interest but not pathognomonic. Rauch and his associates and Shohl, May and Shwachman have taken the excessive nitrogen in the feces to be an important point in diagnosis. Glucose tolerance tests reveal a low type of curve. Tests for vitamin A absorption show impairment.

Blackfan and May<sup>5</sup> and others have reported that roentgenologic studies in cases of fibrocystic disease of the pancreas show the small bowel pattern suggestive of a deficiency state described by Snell and Camp.<sup>25</sup> This consists of delayed motility and alterations in the mucosal relief of the small intestine, with smoothing of the contours of the lumen, obliteration of the usual markings of the *valvulae conniventes* and clumping of the barium in

elongated masses. It is true that such an appearance may be obtained in fibrocystic disease but it must be kept in mind that other conditions can produce this picture, and among them idiopathic steatorrhea. Golden<sup>11</sup> stated that before the age of 1 month, and frequently up to 3 or 4 months of age, the normal small bowel pattern is identical with that of a deficiency state in older children. Neuhauser<sup>21</sup> warned that this appearance in infants must not be falsely interpreted as evidence of fibrocystic disease of the pancreas. Thus the roentgenologic examination of the small bowel is of limited value in this condition.

Neuhauser<sup>21</sup> has described the roentgenologic appearance of the abdomen in infants with meconium ileus and by his criteria he has been able to make a correct diagnosis in 4 of the last 10 cases that he has seen. In those cases in which no definite roentgenologic diagnosis could be made, there was only evidence of intestinal obstruction as shown by marked dilatation of loops of small bowel with gas and fluid levels in the small bowel when the patient was in the erect position. This picture simulates that produced by atresia or marked stenosis of the ileum. In those in which the roentgenologic diagnosis of meconium ileus could be made the appearance was different and, according to Neuhauser, typical of that condition. The small bowel was distended without abrupt termination of the visualized gas. Small and minute bubbles of gas could be seen throughout the distal part of the small bowel. These were apparently caused by small quantities of gas being forced into the tenacious mucilaginous meconium. This distal portion of the bowel was somewhat smaller in caliber than that which was well distended with gas. By these criteria more cases of meconium ileus may be diagnosed in the future.

Osteoporosis has been reported rather consistently in fibrocystic disease of the pancreas. It is considered to be due to vitamin D deficiency or lack of calcium or both. It is remarkable that rickets is found so infrequently.

A review of the reported cases of fibrocystic disease of the pancreas revealed that roentgenograms of the thorax have been used frequently to confirm the clinical evidence of respiratory infection. As a rule, however, no detailed report of the roentgenologic appearance of the lungs has been given, it has merely been stated that the roentgenograms revealed pulmonary infection. In view of the prominent part that respiratory infection plays in this disease, it is surprising that more attention has not been paid to the roentgenologic aspect.

Attwood and Sargent<sup>2</sup> in 1942 described pulmonary changes in fibrocystic disease of the pancreas as seen in the roentgenogram. They reported a diffuse pathologic process involving all lobes of both lungs which was most marked at the hilus and decreased in intensity toward the periphery. These roentgenologic changes suggested a chronic or subacute process rather than an acute change. They noted that in contrast to ordinary bronchopneumonia the changes in the upper parts of the lungs were as marked as in the bases. Repeated roentgenographic examinations revealed the chronic character of the pulmonary changes. They found atelectasis in a certain percentage of cases. These pulmonary changes were observed also by Menten and Middleton.<sup>18</sup> Baylin<sup>4</sup> noted also persistent mottling at the bases; a honeycomb-like picture in the lower part of the lungs coupled with linear streaks that followed the bronchial pattern and was suggestive of bronchiectasis.

In 1943 Neuhauser<sup>20</sup> made a careful study of the roentgenograms in cases of this type and again in 1944.<sup>21</sup> He divided the pulmonary changes

into two stages. The first stage is characterized mainly by emphysema and atelectasis, dependent on the partial or complete obstruction of the bronchi or bronchioles. He noted that lobular atelectasis is difficult to distinguish from pneumonic consolidation. Lobar atelectasis is more easily identified. Obstructive emphysema, he found, was not difficult to identify; it produced increased radiolucency of the lung and widening of the interspaces with, perhaps, bulging. In the second stage infection is superimposed. In this stage hilar shadows are accentuated and bronchovascular markings are increased symmetrically. There are multiple areas of peribronchial infiltration which may be confluent and suggestive of pneumonia. Bronchiectasis is often present but he found, as have others, that it is difficult to identify without the use of lipiodol, which is not warranted. The ultimate roentgenologic appearance in a patient with long-standing disease is one of pulmonary emphysema with areas of atelectasis. There is diffuse pulmonary infection consisting of peribronchial pneumonia, bronchiectasis and bronchiectatic abscesses. The changes in the lungs are widespread, involve the apices and bases and extend to the periphery. As a rule there is no pleural reaction. ♦

The pulmonary changes described by Neuhauser have been confirmed by Merner and Bosma.<sup>19</sup> They, too, emphasized the frequency with which emphysema and atelectasis are found associated with widespread pulmonary infection on roentgenologic examination.

Neuhauser's description is outstanding; with his correlation of the roentgenologic aspects of the pulmonary changes with the well-established clinical and pathologic picture. Atelectasis and emphysema with superimposed infection are the usual findings at necropsy. Neuhauser has shown that these changes can be seen in the roentgenogram before death.

As the result of his roentgenologic observations, Neuhauser has said: "It is to be assumed that this appearance is not pathognomonic, but the recognition of a long standing pulmonary disease characterized by obstructive emphysema, atelectasis, fibrosis, and widespread infection involving all lobes is sufficient to warrant a tentative diagnosis of pancreatic fibrosis to be confirmed by examination of the enzyme activity of the duodenal juice." Merner and Bosma also considered the pulmonary changes fairly characteristic and of great assistance in diagnosis. These opinions seem to be warranted. It is expected that this diagnosis will be suggested by roentgenologists more frequently in the future and it is hoped that as a result of this, the antemortem diagnosis will be made with greater accuracy.

In 8 of the last 10 cases of fibrocystic disease of the pancreas seen by Neuhauser, the roentgenologic diagnosis has been correct. Markel<sup>17</sup> reported 1 case in which the diagnosis was first suggested by the roentgenologist. In this case the celiac syndrome was slight and had not been noted until the roentgenograms of the thorax revealed changes which were suggestive of those found associated with fibrocystic disease of the pancreas.

**Summary.** It may be stated that fibrocystic disease of the pancreas is a disease entity characterized by the celiac syndrome and chronic respiratory infection. There is pancreatic insufficiency and the most important diagnostic procedure is examination of the duodenal contents for evidence of pancreatic achylia. Symptoms of respiratory infection often predominate and roentgenologic examination of the thorax may reveal pulmonary changes that are rather characteristic of this disease. Meconium ileus may be diagnosed, at times, by the roentgenologic examination of the abdomen.

## REFERENCES

- (1.) Andersen, D. H.: *Am. J. Dis. Child.*, 56, 344, 1938. (2.) Attwood, C. J., and Sargent, W. H.: *Radiology.*, 39, 417, 1942. (3.) Baggenstoss, A. H., and Kennedy, R. L. J.: *Am. J. Clin. Path.*, 15, 64, 1945. (4.) Baylin, G. J.: *Am. J. Roentgenol.*, 52, 303, 1944. (5.) Blackfan, K. D., and May, C. D.: *J. Pediat.*, 13, 627, 1938. (6.) Blackfan, K. D., and Wolbach, S. B.: *J. Pediat.*, 3, 679, 1933. (7.) Daniel, W. A., Jr.: *Am. J. Dis. Child.*, 64, 33, 1942. (8.) Farber, S.: *New England J. Med.*, 229, 653, 682, 1943. (9.) Farber, S.: *Arch. Path.*, 37, 238, 1944. (10.) Gee, S.: *St. Bartholomew Hosp. Rep.*, 24, 17, 1888. (11.) Golden, R.: *Radiology*, 36, 262, 1941. (12.) Harper, M. H.: *Arch. Dis. Child.*, 13, 45, 1938. (13.) Hurwitt, E. S., and Arnheim, E. E.: *Am. J. Dis. Child.*, 64, 443, 1942. (14.) Jeffrey, F. W.: *Canad. Med. Assn. J.*, 45, 224, 1941. (15.) Kaufmann, W. and Chamberlin, D. B.: *Am. J. Dis. Child.*, 66, 55, 1943. (16.) Landsteiner, K.: *Centralbl. f. allg. Path. u. path. Anat.*, 16, 903, 1905. (17.) Markel, I. J.: *J. Indiana Med. Assn.*, 37, 674, 1944. (18.) Menten, M. L., and Middleton, T. O.: *Am. J. Dis. Child.*, 67, 355, 1944. (19.) Merner, T. B., and Bosma, J. F.: *Bull. Staff Meet., Hosp. Univ. Minnesota*, 16, 393, 1945. (20.) Neuhauser, E. B. D.: Quoted by Farber, S<sup>s</sup> (21.) Neuhauser, E. B. D.: Unpublished data. (22.) Parmelee, A. H.: *Am. J. Dis. Child.*, 50, 1418, 1935. (23.) Rauch, S. Litvak, A. M., and Steiner, M.: *J. Pediat.*, 14, 462, 1939. (24.) Shohl, A. T., May, C. D., and Shwachman, H.: *J. Pediat.*, 23, 267, 1943. (25.) Snell, A. M., and Camp, J. D.: *Arch. Int. Med.*, 53, 615, 1934. (26.) Wolman, I. J.: *AM. J. MED. SCI.*, 203, 900, 1942.

# BOOK REVIEWS AND NOTICES

---

PUBLIC MEDICAL CARE. Principles and Problems. By FRANZ GOLDMANN, M.D. Pp. 226. New York: Columbia Univ. Press, 1945. Price, \$2.75.

PUBLIC medical care is defined as being medical care supported by funds obtained by taxation and administered by a governmental agency. The book is written from the point of view that "adequate medical care is a fundamental human right. It is as much a necessity of life as food, shelter, clothing, or education. It is no less indispensable to the well-being of society than to the welfare of the individual." With such a premise, it is inevitable that the extensive study on which this book is based would reveal many inadequacies in the present status of public medical care. In fact, the first and major part of the book entitled "Haphazard Growth," is largely concerned with the existing problems of public medical care, while in each chapter the progress of haphazard growth is traced.

After a short discussion of the pattern of progress, the developments of public medical care are described and analyzed in chapters on the growth of public hospitals, the evolution from the "free dispensary" to the public medical center, the development of programs of public medical care for "persons in need" and the present framework of administration of public medical care.

The second part of the book is entitled "Directed Growth," and is a discussion of the planning for hospitals and related facilities, for the organization of professional services, for the payment for facilities and services and for the administration of medical care, closing with a section on the underlying philosophy of medical care.

The book is an attempt to give a composite picture of public medical care as a social movement. It is written with a background of knowledge of the problems of other countries, as well as of our own, and exhibits a careful and documented study carried on with a broad and comprehensive view of the relation of health to social security and economic welfare.

It is clearly demonstrated that the haphazard growth of medical care that has taken place in this country has resulted in administrative confusion and lacks system or unity, and the conditions have led many who have seriously studied the problems of public medical care to agree that "the house urgently needs rebuilding from bottom up." The book serves a useful and important purpose by bringing into a clear light the present deficiencies of public medical care in relation to the possible value of modern medicine both for the individual and for society as a whole.

In the second part of the book, on planning for medical care, the author has presented sound and forward-looking ideas which conform with those that are now rapidly taking shape in planning a National Health Service as a component of social security. He, therefore, directs attention to the fundamental problems involved in a wide coverage of the population by public medical care, and points out the desirability of centralized control with localized administration in the planning of medical care. This book should be given careful consideration by both laymen and members of the health professions who are called upon to participate in the field of health organization. It is a field in which all intelligent people should have an interest; because, as quoted from Sir Arthur Newholme, "The health of every individual is a social concern and responsibility" as "medical care in its widest sense for every individual is an essential condition of maximum efficiency and happiness in a civilized community."

G. R.

**PENICILLIN AND OTHER ANTIBIOTIC AGENTS.** By WALLACE E. HERRELL, M.D., M.S., F.A.C.P., Assistant Professor of Medicine, the Mayo Foundation, University of Minnesota; Consultant in Medicine, Mayo Clinic, Rochester, Minn. Pp. 348; 45 figs.; 45 tables. Philadelphia: W. B. Saunders, 1945. Price, \$5.00.

THIS monograph deals fully with the preparation, properties, and uses of penicillin and similar agents. Published at a time when optimal dosage for the treatment of many diseases is still a matter to be determined, it can be used only as an introduction to therapy, lest one fall into serious error.

W. J.

**DIETOTHERAPY. CLINICAL APPLICATION OF MODERN NUTRITION.** Edited by MICHAEL G. WOHL, M.D., Associate Professor of Medicine, Temple University School of Medicine; Chairman, Advisory Committee on Nutrition, Philadelphia Department of Public Health. Pp. 1029; 92 figs., numerous tables and charts. Philadelphia, W. B. Saunders, 1945. Price, \$10.00.

A BOOK as inclusive as this one can be recommended as a source of ready reference. The importance of various elements of diet is considered fully in relation to normal nutrition, periods of "physiologic stress," and many medical and surgical disorders. The 44 sections have been written by 58 contributors. The material is well organized, and is enhanced by an adequate index and bibliography. The reader might even be warned against becoming engrossed to the extent that he forget therapeutic measures other than food and vitamins.

W. J.

**TRAUMA IN INTERNAL DISEASES.** By RUDOLPH A. STERN, M.D., Asst. Attending Physician, City Hospital, New York, N. Y. Pp. 590. New York: Grune & Stratton, 1945. Price, \$6.75.

THE part that trauma may play in causing or aggravating internal diseases is always a perplexing problem. Legal aspects of these questions, often scientifically insoluble, must be decided by the courts; however, that justice may be best served, it is important that all facts be readily available. Dr. Stern's book is a critical compilation of important case histories and experimental work bearing on these diseases. As such it helps fill a gap in the literature in English.

In the introduction the author discusses the problems and common errors of rendering testimony in medico-legal cases. Then follows a systematic recital of various diseases, with abundant documentation from the medical and legal literature. The examples used are chosen either because they carry weight as scientific evidence or because they demonstrate the courts' demonstrated attitude in such cases.

There is a good bibliography. The printing is good but the quality of paper and binding show the effect of wartime shortages.

This book will be most useful to practitioners who must give evidence and express expert opinion in the courts and to lawyers who deal with such cases.

W. S.

**EFFECTIVE LIVING.** By C. E. TURNER, A.M., Ed.M., Sc.D., Dr.P.H., Professor of Public Health, Massachusetts Institute of Technology; formerly Assoc. Professor of Hygiene, Tufts Medical and Dental Schools; and ELIZABETH McHOSE, B.S., M.A., Director of Physical Education for Girls and Chairman of the Health Council, Senior High School, Reading, Pa. Second Ed. Pp. 432; 164 ills. St. Louis: Mosby, 1945. Price, \$2.00.

THE authors' aim is to help youth discover ways of effective living, which they interpret as the development of one's maximum capacity as an individual, as a member of the family group, and as a useful citizen. Much factual material is included in simple terms which are rendered still more comprehensible by a full Glossary. Any youth who has sympathetically studied and assimilated the wisdom in these 400 small pages will necessarily be greatly aided toward the triple goal. Most of us would scoff, however, at the hope of



getting any number of youth to do just this, were it not for the experiences of the authors in the class room and the success that they seem to have met in at least 2 high schools. Caveat criticus!

E. K.

**THE HUMAN BODY.** By LOGAN CLENDENING, M.D., Professor of Clinical Medicine, University of Kansas. Fourth Ed. Pp. 443; 106 figs. New York: Alfred A. Knopf, 1945. Price, \$4.00.

THIS little book remains a readable introduction to medicine for the laity. It contains some misstatements of fact, however, and might be criticized by voracious readers of the news magazines as being a little out of date. W. J.

**THE STORY OF A COUNTRY MEDICAL COLLEGE.** A History of the Clinical School of Medicine and The Vermont Medical College, Woodstock, Vt., 1827-1856. By FREDERICK CLAYTON WAITE. Pp. 213. Montpelier, Vt.: Vermont Historical Society, 1945. Price, \$4.50.

As the author points out, the major importance of this book is that it is the first history of a country medical college to be published. They had characteristics quite different from those of urban medical colleges. One third of all the medical colleges founded before the Civil War were country medical colleges and not far from one-third of all the men who attended any medical college before 1861 went to a country medical college. For Vermonters it has the added local interest of details (including a catalogue of faculty and students) about one of the state's influential educational institutions, successful in its day but "almost forgotten in the 88 years since it closed." We read of the College's foundation by Dr. Joseph A. Gallup in 1827, of his frustration by younger associates leading to his resignation after 8 years, of its temporary affiliations with 2 colleges of Arts (Waterville, Middlebury), of its 18 years of independent existence, and 20 years of coöperation with another school, of such items as the difficulties in teaching anatomy, and dissensions in the faculty, that have a familiar ring for the larger as well as the smaller schools. French methods of physical diagnosis were brought to the Vermont Medical College by Alonzo Clark in 1842, experimental mammalian physiology (gastric fistulas in dogs *au Beaumont*) by J. C. Dalton, Jr., in the fifties. But medical education was already concentrating in the larger centers where clinical instruction was available and in 1857 decreasing attendance caused the resignation of the faculty and brought an end to our story.

The author has performed a "labor of love" satisfactorily, as was to be expected from his well-rounded education and previous historico-literary activities and affiliations.

E. K.

**THE HISTORY OF SURGICAL ANESTHESIA.** By THOMAS E. KEYS. With an Introductory Essay by CHAUNCEY D. LEAKE, and a concluding chapter, The Future of Anæsthesia, by NOEL A. GILLESPIE. Pp. 191. New York: Schuman's, 1945. Price, \$6.00.

DR. KEYS appropriately begins his admirable special history with an illustration from the Nuremberg Chronicle of the first recorded anesthesia—the "deep sleep" that fell upon Adam when Eve was brought forth from his side. From then on, the same entertaining point of view carries us, both pleasantly and authoritatively, rapidly through the early stages (28 pages from "the beginnings" to Morton), with the bulk of the text devoted to the last 100 years. The 16 parts of Section I deal separately with a number of general and local anesthetics, "twilight sleep," anoci-association, various modes of administration (rectal, caudal, intravenous, endotracheal, etc.), apparatus, and physiologic and pharmacologic factors. One of the most praiseworthy features of the book, a feature which indeed sets a high standard for other special subject histories to emulate, is the rich bibliography offered in quadruple form (references for Section I, a chronologic list, a list by subject, then by author) which greatly increases its value for those seeking sources in

this field. The 77 pages that they occupy are well spent, even in these days of paper shortage, and testify to the painstaking scholarly nature of the whole volume. The interesting personalized Introductory Essay by Leake—himself a distinguished maker of anesthesia history—together with N. A. Gillespie's comments on The Future of Anesthesia, and Fulton's Appendix on the Morton and Warren Tracts on Ether (Letheon) add still further to the value and interest of this excellent production. The Reviewer wishes to add a final word on the advantages accruing from the excellent qualifications of those who contributed to the contents of the book and from their easy access to the greatest of medical libraries. E. K.

---

**THE AVITAMINOSES.** The Chemical, Clinical and Pathological Aspects of the Vitamin Deficiency Diseases. By WALTER H. EDDY, PH.D., Emeritus Professor of Physiological Chemistry, Teachers College, Columbia Univ.; and GILBERT DALLDORF, M.D., Pathologist of the Grasslands and Northern Westchester Hospitals, Westchester County, N. Y.: Third Ed. Pp. 438; numerous plates and tables. Baltimore: Williams & Wilkins, 1944. Price, \$4.50.

This well-known treatise on the avitaminoses is now in its 3rd edition. It has been carefully revised; the chapter on the mode of behavior of the vitamins has been rewritten. The chemistry and nature of the individual vitamins, the pathology of experimental avitaminoses and of the clinical deficiencies is presented in detail. An excellent bibliography is appended. Tables of the vitamin values of foods and laboratory tests for the recognition of deficiency states are also included. E. W.

---

**ANNUAL REVIEW OF BIOCHEMISTRY, Vol. 14.** Edited by JAMES MURRY LUCK and JAMES H. C. SMITH. Pp. 856. California: Annual Reviews, Inc., Stanford Univ. P. O., 1945. Price, \$5.00.

The new 14th volume of the "Annual Review of Biochemistry" maintains the high standard of its predecessors in this review series, which has become invaluable to all interested in biochemical advances. This is the last of the so-called "war" volumes, and, in spite of obstacles which certain reviewers experienced in securing literature from distant sources, it is the largest volume thus far published.

There are 28 individual reviews by experts in the chosen fields. Such topics, commonly reviewed as Biological Oxidations and Reductions, The Chemistry of Carbohydrates, Lipids, Amino Acids and Proteins, and the Metabolism of these constituents (reviewed separately), are once again covered.

Reviews upon more unusual topics are by J. M. Gulland and colleagues (nucleic acids and nucleoproteins), I. Fankuchen (an excellent review on x-ray studies of compounds of biochemical interest), C. R. Noller (the terpenes), W. L. Ruigh (steroids), W. T. Salter (hormones), J. P. Greenstein (biochemistry of malignant tissues), and J. H. Mueller and A. E. Oxford respectively on the timely subjects of The Chemistry and Metabolism of Bacteria, and The Chemistry of Antibiotic Substances other than Penicillin. D. D.

---

**COLLOID CHEMISTRY.** Theoretical and Applied. Edited by JEROME ALEXANDER. Pp. 1256; numerous figs. and tables. New York: Reinhold Pub. Co., 1944. Price, \$20.00.

This volume, which is the 5th in the series, is arranged in 2 sections, the 1st dealing with the theory and methods of colloid chemistry, the 2nd with its applications to biology and medicine. There are included some 60 essays varying in length from 5 to 90 pages, each dealing with the present status of, and recent developments in each special field.

In the 1st section are contained 25 authoritative articles by such experts

as Harkins (on surface films), McBain (on soaps and detergents), Germer (on applications of electron diffraction), Huggins (on x-ray analysis), Hickman (high-vacuum distillation), Mark (polymerization), MacInnes and Longworth (electrophoresis of proteins and related substances), and Pickels (high speed centrifugation). Other topics deal with microradiography of colloidal materials, the electron microscope, elasticity of rubber and similar materials, the vitreous state, sonic and ultrasonic waves in colloid chemistry, the cyclotron and betatron, selective adsorption, and numerous other topics.

In the biologic field excellent articles are presented by Astbury (proteins), Rothmund (photosynthesis), Farr (plant cell membranes), Hixon and Rundle (advances in starch chemistry), Axelrod and Elvehjem (enzymes and biological action of vitamins), Lauffer and Stanley (colloid chemistry of purified viruses), Barth (colloid chemistry of embryonic development), Chambers (physical properties of protoplasm), Meyerhof (physical changes in muscular activity), Landis (the capillary circulation), Menkin (inflammation), Boyd (immunology), Cannon (homeostasis), Loeb (cancer), and Carlson (gerontology). This list is incomplete but represents a fair cross-section of the material covered in this huge volume. Undoubtedly other articles will appeal to different readers.

It is perhaps unfortunate that this single volume encompasses such a wide range of topics. Nearly every scientist will find some of these articles stimulating, but it seems hardly likely that many will be sufficiently interested in all or most of these topics to purchase such an expensive volume. The editor has, however, contributed a distinct service. Here in excellently presented form is an authoritative discussion and correlation of the fundamental phenomena of colloid chemistry and biology.

S. G.

**THE ABORTION PROBLEM.** Proceedings of the Conference held under the auspices of the National Committee on Maternal Health, June 1942. HOWARD C. TAYLOR, JR., M.D., Conference Chairman. Pp. 182. Published for the National Committee on Maternal Health. Baltimore: Williams & Wilkins, 1944. Price \$2.50.

THIS volume deals with the magnitude of the abortion problem, spontaneous abortion and its prevention, the social, moral and economic causes and control of abortion, and a summary and the recommendations of the conference. There are between 3000 and 4000 deaths a year in this country due to abortion, and the death rate from this cause appears to be changing very little if at all. About 30% of maternal deaths are due to this cause.

The papers and the discussions forming the substance of this volume are excellent and make interesting and instructive reading. The recommendations are conservative and sound. The volume is recommended to all who are interested in the problem of abortion.

D. M.

**DISEASES OF THE BREAST.** By CHARLES F. GESCHICKTER, M.A., M.D., Lt. Comdr., MC, USNR, Director of The Francis P. Garvan Cancer Research Laboratory; Pathologist, St. Agnes Hospital, Baltimore. With a Special Section on Treatment in collaboration with MURRAY M. COPELAND, A.B., M.D., F.A.C.S., Instructor in Surgery, Johns Hopkins Medical School. Second Ed. Pp. 826; 593 ill. Phila.: Lippincott, 1945. Price, \$12.00.

THIS 2nd edition represents a considerable expansion of the original volume. The section dealing with mammary carcinoma has been brought up to date and enlarged. The chapter on the Mechanism of Tumor Formation has been entirely rewritten. New material includes the use of penicillin for infectious mastitis, endocrine therapy in chronic cystic mastitis, the criteria of operability and inoperability of mammary carcinoma.

In the chapter on The Mechanism of Tumor Formation, the author dwells entirely upon the rôle of estrogenic hormones, stating that "... the sequence of estrogenic response on the part of the mammary gland may be

considered as highly significant. The changes leading up to cancer may be looked upon as essential steps in the cancer process and as forming a definite pattern for the development of malignancy in any tissue, regardless of the means employed to induce it. In the belief that the latter interpretation is correct, the sequence of estrogenic effects will now be summarized etc." Whereas this concept is acceptable as a working hypothesis, more especially in regard to breast tumors, its wholehearted acceptance must await confirmation. At present many investigators of neoplastic processes would regard such a stand as untenable.

The volume is conveniently arranged, well illustrated, and readable. It contains a wealth of material for the clinician, surgeon and pathologist; a valuable addition to anyone's medical library.

D. C.

**THEORY OF OCCUPATIONAL THERAPY.** By NORAH A. HAWORTH, M.A. (CANTAB.), M.R.C.S., L.R.C.P., D.P.M., Assistant Medical Officer, London Passenger Transport Board; late Medical Officer, Horton Emergency Hospital; and Senior Assistant Medical Officer, Severalls Mental Hospital, Colchester; and E. MARY MACDONALD, Prin., Dorset House School of Occupational Therapy, Barnsley Hall Emergency Hospital, Bromsgrove; Member of the Association of Occupational Therapists. Second Ed. Pp. 148; 68 figs. Baltimore: Williams & Wilkins, 1944. Price, \$2.50.

This book gives a fairly good general picture of all phases of occupational therapy. It would be, in the opinion of the Reviewer, instructive for those who are little acquainted with the work; but to those in the field it presents nothing more than a neat compilation of facts already known. Another criticism is that it does not treat adequately the needs of the present-day program in a military hospital, at least, in this country. New crafts and new theories are being worked out in these hospitals every day; yet, little mention is made of them.

In the chapters describing the adaptation of equipment for specific treatment, many excellent ideas are given; but it seems to the Reviewer that such a complete change of the machinery would make occupational therapy so bizarre that it might well produce a poor psychologic effect on the patient.

C. W.

**SEGMENTAL NEURALGIA IN PAINFUL SYNDROMES.** By BERNARD JUDOVICH, B.S., M.D., Instructor in Neurology, Graduate School of Medicine, University of Pennsylvania; Clinical Instructor in Neurology, Women's Medical College; Chief of Neuralgia Clinics, Philadelphia General Hospital, Graduate Hospital, and Women's Medical College Hospital; and WILLIAM BATES, B.S., M.D., F.A.C.S., F.I.C.S., Professor of Surgery, Graduate School of Medicine, University of Pennsylvania; Consulting Surgeon, Babies' Hospital and Philadelphia Home for Incurables; Consulting General Surgeon, Wills Hospital, Phila. Pp. 313; 178 ills. Phila.: Davis, 1944. Price, \$5.00.

This monograph develops a single theme, simply, effectively and forcefully. The interpretation of pain is a task of every physician whether specialist or general practitioner, and the authors present observations which should help physicians in this task. As stated in the Preface, "the interpretation of pain can be greatly facilitated by eliciting hyperalgesic or tender skin zones. The combination of segmental pain and tenderness appears to be due to factors which irritate roots, ganglia, or trunks of the spinal sensory nerves, and not due to painful impulses originating in diseased viscera."

Whether or not this thesis is correct, it demands the attention of neurologists, neurosurgeons, and anesthesiologists, all of whom are directly concerned with the relief of pain. It can also be read profitably by the average physician, since diagnostic as well as practical therapeutic suggestions are offered in detail.

For a volume published in wartime the paper, type and illustrations are satisfactory. They do not compare, however, with pre-war standards.

R. D.

**THE CHEMICAL FORMULARY.** A Collection of Valuable, Timely, Practical Commercial Formulæ and Recipes for Making Thousands of Products in Many Fields of Industry, Vol. VII. Editor-in-Chief, H. BENNETT. Pp. 474. Brooklyn: Chemical Publishing Co., 1945. Price, \$6.00.

THIS volume, the 7th in the series, contains more than 2000 formulas for mixing and making products ranging from adhesives to rust preventatives and from cold creams to roach killers. Farmers, both amateur and professional, will find here directions for preparing insecticides, fertilizers and livestock medicines at low cost. There is useful information for the photographer, painter, chemist, as well as the housewife. Material covered here includes adhesives, flavors and beverages, cosmetic and drug products, emulsions and colloids, farm and garden specialties, food products, inks, leather, lubricants and oils, construction materials, metals and alloys, paint, varnish and lacquers, paper, photography, polishes, explosives, plasters, resins, rubber, wax, soaps and cleaners, textiles as well as a number of miscellaneous articles.

The directions for using the formulas are simple and direct, as this volume, in contrast to previous volumes, has been written for laymen. This work will be a storehouse of information to persons in all walks of life. S. G.

**AN INDEX OF DIFFERENTIAL DIAGNOSIS OF MAIN SYMPTOMS.** By Various Writers. Edited by HERBERT FRENCH, C.V.O., C.B.E., M.A., M.D. (Oxon.), F.R.C.P., Consulting Physician Guy's Hospital; late Physician, H.M. Household. Assisted by ARTHUR H. DOUTHWAITE, M.D., F.R.C.P., Physician, Guy's Hospital; Honorary Physician, All Saints' Hospital for Genito-urinary Diseases. Pp. 1128; 798 ill. of which 231 are colored. Sixth Ed. Baltimore: Williams & Wilkins Co., 1945.

THIS book offers a ready reference on the application of differential diagnosis to all the main signs and symptoms of disease. All-symptoms and signs that are encountered on the examination of a patient are adequately listed, and a short note about various disease complexes in which they may occur are discussed briefly and concisely. This edition has only a few changes from the fifth. The number of colored plates has been increased and several sections rewritten. More note is also given to that group of disease that has gained added importance because of the war. J. F.

**PSYCHIATRY IN MODERN WARFARE.** By EDWARD A. STRECKER, A.M., M.D., Litt.D., LL.D., Professor of Psychiatry, School of Medicine, University of Pennsylvania; Consultant to the Surgeon-Generals of the Army and the Army Air Forces, the Navy and the U. S. P. H. S.; and KENNETH E. APPEL, Ph.D., M.D., Sc.D., Assistant Professor of Psychiatry and Chief of Clinic, School of Medicine, University of Pennsylvania; Lecturer in Psychiatry, School of Neuropsychiatry, U. S. Navy, etc. Pp. 88. New York: Macmillan, 1945. Price, \$1.50.

At a recent meeting, a summary of a comparative study of the two World Wars was so generously received that copies were requested, and the authors now offer this brief treatise. Part I contains Psychiatry and the Two World Wars: Contrasts in the Nature of War; Organization of Neuropsychiatry; Psychological Effects on Civilians; Symptomatology; Psychopathology; Treatment; Prognosis; The Increase in Mental Disorders. Part II covers Demobilization and the Return to Civilian Life; Civilian Shares Responsibility for Readjustment; Every Soldier Has a Readjustment Problem; The Philosophy of Readjustment; Methods of Helping Returning Service Men; Improved Veteran.

World War II was global in extent, with new engines of war and methods of destruction. Robot bombs and communication through electromagnetic waves are sent from and received by portable apparatus. Danger at the rear as well as at the front is now great, and civilian populations are a part of the conflict. Increase in the surprise element causes greater fear. The belief that

the lessons of the previous war would decrease the number of neuroses was not substantiated—psychiatrists, the military and people all being responsible. Hypno-narco-analysis is employed. Evipan is used to penetrate amnesias, evipan and pentothal for narcoanalysis. "Group therapy removes the feeling of isolation, minimizes the feelings of queerness, difference, etc. . . ." Preventive psychiatry is successfully employed. It is emphasized that the "*vast majority of military neuropsychiatric diagnoses do (sic) not signify an incapacity to become an effective worker.*" Psychiatric conditions are now so common that "one-third of the physicians in the country should be psychiatrists or able to treat psychiatric conditions intelligently." N. Y.

---

TEXTBOOK OF ANÆSTHETICS. By R. J. MINNITT, Trinity College, Cambridge, M.D. (Liverpool), D.A. (R.C.P. & S. Eng.) Lecturer in Anæsthesia, University of Liverpool, and JOHN GILLIES, M.C., M.B., CH.B. (Edinburgh), D.A. (R.C.P. & S. Eng.) Consultant in Anæsthetics, Department of Health for Scotland. With a chapter on Local and Regional Analgesia by L. B. WEVILL, M.B., F.R.C.S. (Ed.), Major R.A.M.C. Sixth Ed. Pp. 487; 199 figs. Baltimore: Williams & Wilkins Co., 1944. Price, \$7.00.

THIS is a completely revised and considerably enlarged version of the "Handbook of Anesthetics" originally written by Ross and Fairlie. The new authors, who are eminently qualified for their task, have undertaken it in much the same fashion as other British anesthesiologists. Thus, there is emphasis on technique, apparatus and minutiae, with less attention to broad principles and fundamental background. Furthermore, the volume represents the English devotion to inhalation anesthesia as contrasted to other well accepted methods of pain relief. Spinal anesthesia, for example, receives but 20 pages in the 487 page book.

A textbook on anesthesia is difficult to write, for there is a small group of qualified physicians, specializing in the field, and a large group who "dabble." The former are concerned with establishing their field on a sound scientific foundation and this type of work is of only passing interest. The latter need guidance and direction. For them this work is primarily intended. It is simple and didactic.

New chapters on trichlorethylene, endotracheal anesthesia, intravenous anesthesia and anesthesia for dentistry have been included. A new chapter on choice of anesthetic is well done.

The book should be read with full realization of its limitations, *i. e.*, a national rather than international outlook, together with a somewhat oversimplified approach. R. D.

---

PULMONARY TUBERCULOSIS IN THE ADULT. Its Fundamental Aspects. By MAX PINNER, M.D., Chief, Division of Pulmonary Diseases, Montefiore Hospital for Chronic Diseases, New York; Editor, American Review of Tuberculosis; Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, New York. Pp. 579. Springfield, Ill.: Charles C Thomas, 1945. Price, \$7.50.

THIS book is a highly valuable contribution to the fundamental understanding of adult pulmonary tuberculosis, its prevention and treatment. Unlike other books addressed to clinicians it presents the essential, pertinent, scientific data on the pathogenesis of the disease in an adequate and integrated manner—a subject which is often dismissed perfunctorily—so that the clinician is left in a scientific desert as far as the practice of the specialty is concerned. The first part of the book is devoted to a consideration of the fundamental aspects of the tubercle bacillus, the histogenesis of the lesions as they occur in man, the rôle of tuberculin, the principles of immune reactions and the factors which control the progression and healing of pulmonary phthisis. While these data have been discussed in other books at greater length, the latter stress animal experimentation and give but scant attention to the practical problems of the human disease. It is true that Dr. Pinner, in presenting

this self-consistent interpretation of the disease as a whole, often expresses personal opinions; they are, however, properly labeled and not introduced with the assumed halo of an *ex cathedra* oracle. On the contrary, attached to each chapter are citations from the literature which give contrary views. This bibliography has the novel and useful advantage in that it appends to each citation a concise statement of the essential nature of the contribution and its evaluation. Then follows a more direct consideration of the primary complex and tuberculosis in children, the classification of pulmonary tuberculosis, where it is stressed that, in evaluation of prognosis, it is not the extent of the disease which is significant, but rather the inherent aptitudes of progression and regression which characterizes the lesion. Excellent Roentgen ray and autopsy photographs illustrate and clarify the text. Special chapters are devoted to tracheobronchitis, diagnostic principles, laboratory procedures and the physiology of respiration and pulmonary collapse. Guides to medical treatment are given in the light of the data on the pathogenesis of the disease previously recorded. The last chapter considers its epidemiology in a penetrating manner.

This book is highly recommended to every clinician as an integration of present knowledge derived not only from American sources. It is restrained in its conclusions and sound in its judgment and appears to me the most acceptable and philosophically integrated book on the subject. M. L.

---

THE ART OF RESUSCITATION. By PALUEL J. FLAGG, M.D., Chairman, Comm. on Asphyxia, Am. Med. Assn.; President and Founder of the Soc. for the Prevention of Asphyxial Death, Inc.; Visiting Anæsthetist, Manhattan Eye and Ear Hospital; Consulting Anæsthetist to St. Vincent's (and other) Hospitals. Pp. 453; 176 figs. N. Y.: Reinhold, 1944. Price, \$5.00.

THERE can be no doubt of the contributions of the author in fixing attention on the hazards of asphyxia long before the medical profession as a whole was aware of these hazards. In recent years, instead of strengthening his position by research and fundamental observations, Flagg has continued to devote his energies to the printed word. This book is the logical outcome of such a career. It represents an extremely important viewpoint without scientific documentation. It is of great interest historically; of less value to the individual challenged by the fundamental problems of resuscitation. Its title is essentially correct representing "The Art"—rather than "The Science of Resuscitation."

In fairness to the author it should be pointed out that his purpose is clearly stated in the preface, "The matter presented herein is elementary. It presents a framework upon which the experiences and the contacts of the author may readily be studied. Should this form and matter prove of interest, the entire subject, it is hoped, will attract the attention and enlist the activities of highly qualified research workers and technicians."

The reviewer recommends this book to physiologists and anesthesiologists, primarily because of its historical importance. It is not recommended to the general reader. R. D.

---

MODERN METHODS OF AMPUTATION. By EDMUNDO VASCONCELOS, Professor, University of São Paulo. With an Introductory Survey of The Development of Amputation by MAJOR GEN. NORMAN T. KIRK, M.C., Surgeon General, U. S. Army. Pp. 253; 258 figs. New York: The Philosophical Library of New York, 1945. Price, \$10.00.

THE book, as Dr. Vasconcelos states, was written for the practitioner and not for the expert. However, the author's 20 years of experience has enabled him to present the material in such a clear and understandable manner that the expert as well as the practitioner can benefit by his presentation of the subject. The technics for the various amputations are discussed in detail with

emphasis on the common mistakes that surgeons may make. Only procedures judged by the author to be of clinical value are included in the volume. The illustrations of technics and levels of amputations are vividly illustrated.

H. Z.

---

FUNDAMENTALS OF ANESTHESIA. An Outline. By Subcommittee on Anesthesia of Division of Medical Sciences, National Research Council. Second Ed. Pp. 231; 81 figs.; 19 tables. Illinois: American Medical Assn. Press, 1944. Price, \$2.50.

THIS is an extremely useful manual on practical anesthesia. Although dogmatic and "stream-lined" in its form, the volume is better than any other on the subject. In this new edition the only additions are extra pages on local and spinal anesthesia, together with 9 new illustrations.

R. D.

---

SURGERY OF THE HAND. By STERLING BUNNELL, M.D., Honorary Member of American Academy of Orthopedic Surgeons, Member of American Association of Plastic Surgeons, and of American Society of Plastic and Reconstructive Surgery, Licentiate of American Board of General Surgery and Plastic Surgery. Pp. 734; 597 ill. Philadelphia: J. B. Lippincott, 1944. Price, \$12.00.

DR. BUNNELL's excellent compilation is one which should be available to and should be studied by every surgeon who deals with any condition of the hand. Its comprehensiveness and detail make it superior to previous treatises on the subject. The first of 4 sections covers developmental, comparative and normal anatomy; the second is a detailed discussion of the healing of tissues and the principles of surgical reconstruction of skin, bones, joints, nerves and tendons. Fractures, dislocations, infections and burns are treated in the third section. The last section deals with congenital deformities, tumors, vasomotor and trophic conditions. The book is a valuable addition to medical literature.

H. Z.

---

NITROUS OXIDE-OXYGEN ANESTHESIA. By F. W. CLEMENT, Major, M.C. (A.U.S.). Formerly Director of Anesthesia at Flower Hospital, The State Hospital for the Insane, Lucas County Hospital, Toledo Dental Dispensary; Anesthetist to Toledo, Mercy and St. Vincent's Hospitals, Toledo, Ohio. Second Ed. Pp. 288; 92 engravings. Philadelphia: Lea & Febiger, 1945. Price, \$4.50.

THIS second edition of a well-known little book still represents a single viewpoint—that of the McKesson school. As such, it continues to be of interest to pharmacologists and anesthesiologists.

As the author states "in this revised edition, the changes are those of detail, rather than alterations, of the original concept of the text." Among the new or revised topics are the more detailed method of administration, the dangers of prolonged anoxia, the mechanism and treatment of shock, the rôle of carbon dioxide and that of the sino-aortic areas in anoxia.

Although many experts are not in agreement with the McKesson-Clement theory of nitrous oxide, this monograph forms a valuable addition to any anesthesia reference list. It is not recommended for the novice.

R. D.

---

MEDICAL CLINICS OF NORTH AMERICA. July, 1945. Mayo Clinic Number. Symposium on Medical Emergencies. Pp. 1067; 160 figs. Phila.: Saunders, 1945. Price, \$16.00.

OF the two symposia in this number, the first covers the treatment of medical emergencies. This title is rather misleading as neurological, dermatological and obstetrical emergencies are also covered.

The other symposium is on subjects of useful and timely interest. Stilwell's clinic on "Post War Aspects of Some Tropical Diseases" was interesting and



instructive. This article "takes the scare" out of the newspaper articles which would have malaria, filariasis and other tropical diseases reaching epidemic proportions with the return of the infected service man. The clinic on Liver Function Tests by J. F. Weir helps untangle some problems of the interpretation of these tests that face the general practitioner. As usual, this issue of "The Clinics" is a worthwhile addition to medical literature. J. F.

**DISEASES OF THE NERVOUS SYSTEM.** Described for Practitioners and Students. By F. M. R. WALSH, O.B.E., M.D., D.Sc., F.R.C.P. (LONDON), Hon. D.Sc., Nat. Univ. Ireland, Physician in charge of the Neurological Dept., University College Hospital, London; Physician to the Neurological Hospital for Nervous Diseases, Queen Square. Fourth Ed. Pp. 360. Baltimore; Williams & Wilkins, 1945. Price, \$4.50.

THIS remains an excellent textbook of Neurology. Dr. Walshe's style and terse description stimulates the reader to continue on and on. As admitted in the preface, condensation of the field is difficult and readers would vary in criticizing the omissions. For example, Pancoast tumor in the differential diagnosis of cervical rib and group psychotherapy in psychoneurosis were outstanding omissions to me. The exceptionally good chapters were those on the Parkinson syndrome and cerebral hemorrhage and thrombosis. The attitude toward the treatment of neurological diseases would be well worth teaching to every medical man. J. T.

**STUDENT'S GUIDE IN NURSING ARTS.** By M. ESTHER McCLAIN, R.N., B.S., M.S., Assistant Professor in Nursing Education, and Instructor in Nursing Arts of the Providence Division of the School of Nursing Education, The Catholic University of America, Washington, D. C. Pp. 407. St. Louis: Mosby, 1945. Price, \$3.00.

THIS loose-leaf guide presents the outline in Nursing Arts as taught in a school of nursing education. Each unit and its individual lessons are introduced with concise objectives. There are excellent references to textbooks on nursing arts for each lesson. Review questions on each unit are placed at the end of the unit as a study help. Space is provided throughout the outline for adding notes. Many of the questions are directed to the techniques used in this particular School of Nursing. Therefore, they do not have meaning elsewhere. The titles of the units are the same as those of the outline in the Course Introduction to Nursing Arts as given in the Curriculum Guide for Schools of Nursing. Because of this and the well systematized table of contents, the guide should prove a useful manual not only to students but to instructors as well. L. S.

## NEW BOOKS

*Trauma of the Central Nervous System.* Proceedings of the Association for Research in Nervous and Mental Disease, December 17 and 18, 1943, New York. Pp. 679; 243 illus. and 44 tables. Baltimore: Williams & Wilkins, 1945. Price, \$8.00.

*Essentials of Clinical Allergy.* By SAMUEL J. TAUB, M.D., Professor of Medicine, Cook County Graduate School of Medicine, Fellow of the American Academy of Allergy, formerly Assistant Professor of Medicine, Rush Medical College, of the University of Chicago. Pp. 198. Baltimore: Williams & Wilkins, 1945. Price, \$3.00.

*Fundamental Principles of Physical Chemistry.* By CARL F. PRUTTON, Ph.D., Professor of Chemistry and Chemical Engineering, Case School of Applied Science and SAMUEL H. MARON, Ph.D., Associate Professor of Physical Chemistry, Case School of Applied Science. Pp. 780. New York: Macmillan, 1944. Price, \$4.50.

- Human Biochemistry.* By ISRAEL S. KLEINER, Ph.D., Professor of Biochemistry and Physiology, New York Medical College, Flower and Fifth Ave. Hospitals; Formerly Associate, The Rockefeller Institute for Medical Research, New York. Pp. 573; 70 illus., 5 color plates. St. Louis: C. V. Mosby, 1945. Price, \$6.00.
- Pulmonary Tuberculosis.* A Handbook for Students and Practitioners. By R. Y. KEERS, M.D. (EDIN.), F.R.F.P.S. (GLAS.), Senior Physician and Medical Supt., Tor-na-Dee Sanatorium; Late Assistant Medical Supt., The British Sanatorium, Montana, Switzerland and B. G. RIGDEN, M.R.C.S. (ENG.), L.R.C.P. (LOND.), First Assistant Medical Officer, Tor-na-Dee Sanatorium. Pp. 273; 124 figs. Baltimore: Williams & Wilkins, 1945. Price, \$5.00.
- Hidden Hunger.* By ICIE G. MACY, Ph.D., and HAROLD H. WILLIAMS, Ph.D., Research Laboratory, Children's Fund of Michigan. Pp. 286. Lancaster, Pa.: Jacques Cattell Press, 1945. Price, \$3.00.
- One Hundred Years of Gynecology (1800-1900).* A Comprehensive Review of the Specialty During Its Greatest Century with Summaries and Case Reports of All Disease Pertaining to Women. By JAMES V. RICCI, A.B., M.D., Clinical Professor of Gynecology and Obstetrics, New York Medical College, Director of Gynecology of the City Hospital, New York. Pp. 651. Philadelphia: Blakiston, 1945.
- Pediatric X-ray Diagnosis.* A Textbook for Students and Practitioners of Pediatrics, Surgery and Radiology. By JOHN CAFFEY, A.B., M.D., Associate Professor of Pediatrics, College of Physicians and Surgeons, Columbia University, Associate Pediatrician and Roentgenologist, Babies Hospital and Vanderbilt Clinic, New York City. Pp. 838; 710 figs. Chicago: Year Book Publishers, 1945. Price, \$12.50.
- Facial and Body Prosthesis.* By CARL DAME CLARKE, Ph.D., Associate Professor of Art as Applied to Medicine, School of Medicine, University of Maryland; Capt., Sanitary Corps, A.U.S., Dept. of Moulage and Prosthetics, Army Medical Museum. Pp. 200; 75 illus. St. Louis: C. V. Mosby, 1945. Price, \$5.00.
- Science and the Planned State.* By JOHN R. BAKER, M.A., D.Phil., D.Sc. Pp. 120. New York: Macmillan, 1945. Price, \$1.75.
- American Pharmacy.* Fundamental Principles and Practices. By RUFUS A. LYMAN, M.D., Editor-in-Chief; Dean, College of Pharmacy, Director, Student Health Service, University of Nebraska, Editor, American Journal of Pharmaceutical Education. Pp. 540; 197 illus. Philadelphia: J. B. Lippincott, 1945. Price, \$8.00.

## NEW EDITIONS

- A Handbook for Dissectors.* By J. C. BOILEAU GRANT, Professor of Anatomy, University of Toronto and H. A. CATES, Associate Professor of Anatomy, University of Toronto. Second Ed. Pp. 390. Baltimore: Williams & Wilkins, 1945. Price, \$2.50.
- Diseases of the Nervous System.* Described for Practitioners and Students. By F. M. R. WALSHE, O.B.E., M.D., D.Sc., F.R.C.P. (LOND.), Hon. D.Sc., Nat. Univ. Ireland, Physician in charge of the Neurological Dept., University College Hospital, London; Physician to the National Hospital for Nervous Diseases, Queen Square. Fourth Ed. Pp. 360. Baltimore: Williams & Wilkins, 1945. Price, \$4.50.
- Recent Advances in Neurology and Neuropsychiatry.* By W. RUSSELL BRAIN, M.A., D.M., (OXON.), F.R.C.P., Physician to the London Hospital and the Maida Vale Hospital for Nervous Diseases, etc., and E. B. STRAUSS, M.A., D.M. (OXON.), F.R.C.P., Physician for Psychological Medicine, St. Bartholomew's Hospital. Fifth Ed. Pp. 363; 32 illus. Philadelphia: Blakiston, 1945. Price, \$5.00.

*Handbook of Physiology and Biochemistry.* By R. J. S. McDOWALL, M.D., D.Sc., M.R.C.P., Professor of Physiology, University of London, King's College. Thirty-eighth Ed. Pp. 898; 305 figs. Philadelphia: Blakiston, 1944. Price, \$6.00.

*Synopsis of Genitourinary Diseases.* By AUSTIN I. DODSON, M.D., F.A.C.S., Richmond, Virginia, Professor of Genitourinary Surgery, Medical College of Virginia. Fourth Ed. Pp. 313; 112 illus. St. Louis: C. V. Mosby, 1945. Price, \$3.50.

*Textbook of Obstetrics.* Designed for the Use of Students and Practitioners. By HENRICUS J. STANDER, M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Cornell University Medical College, Obstetrician and Gynecologist-in-Chief, New York Hospital and Director of the Lying-in Hospital, New York City. Third Revision. Pp. 1287; 973 illus. New York: D. Appleton-Century, 1945. Price, \$10.00.

*A Text-book of Pharmacognosy.* By GEORGE EDWARD TREASE, B. Pharm., Ph.C., F.R.I.C., F.L.S., Lecturer on Pharmacognosy and Acting Head of the School of Pharmacy in the University College of Nottingham. Fourth Ed. Pp. 799; 268 figs. Baltimore: Williams & Wilkins, 1945. Price, \$7.50.

#### CORRECTION

We regret that the following article was omitted from the Table of Contents in the October issue:

Use of a Simple Postural Test in Neurocirculatory Asthenia . . . . . 511  
By MAJOR WILLIAM A. JEFFERS, M.C., A.U.S., CAPT. SAMUEL C. SHEIMAN, M.C., A.U.S., and LT. COL. GEORGE H. O'BRASKY, M.C., A.U.S.

#### NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMHAAER, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles, arranged alphabetically according to the name of the first author and should be complete that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

During the emergency 150 REPRINTS will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150.

#### To the Subscriber to

#### The American Journal of the Medical Sciences

Due to the increased costs of material and labor, we find it necessary to increase the subscription price of THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES to \$7.00 per annum. This is the first increase in price since 1920, when it cost \$5.00 a year, the price that was established at its origin in 1820.

The new rates, effective January 1, 1946, will be \$7.00 in the United States, in South and Central America; with \$96 extra for postage in Canada and all other countries.

All new subscriptions and renewals for the year 1946 received with payment up to and including December 31, 1945 will be accepted at the present rate of \$6.00.

We regret the necessity of making this change in price and we shall thank you for your continued patronage.

Very truly yours,  
LEA & FEBIGER,  
Publishers.

# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

DECEMBER, 1945

## ORIGINAL ARTICLES

### CONVALESCENCE FROM SURGICAL PROCEDURES\*

#### I. STUDIES OF THE CIRCULATION LYING AND STANDING, OF TREMOR, AND OF A PROGRAM OF BED EXERCISES AND EARLY RISING

BY ISAAC STARR, M.D.

AND

ROBERT L. MAYOCK, M.D.

PHILADELPHIA, PENNSYLVANIA.

(From the Hartzell Research Department of Therapeutics: The Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania; and The Surgical Clinic of the Hospital of the University of Pennsylvania)

AFTER any operative procedure the patient for a time is obviously abnormal. He does not feel as he did in health, and he is unable to perform certain tasks which in health would be easy for him. Nevertheless, the routine hospital studies disclose nothing abnormal during this period of convalescence.

The purpose of this investigation was to search for objective abnormalities during convalescence from surgical procedures; by available special techniques, and by other methods which we might devise. If we could discover objective abnormalities they might be used as a test for the duration of convalescence and also as a means of judging the success or failure of attempts to shorten it, which were also part of our project.

In planning the work we expected that few abnormalities would be found when convalescent subjects were studied at rest, but we also expected that, by having them perform a task, abnormalities might well be discovered. For such a test, preferring tasks that our patients were accustomed to, we chose the following: the first test consisted of observing the changes in the circulation which took place on arising, the second, of studying the effects of mild exercise produced by pushing up and lowering a weight. Our results with the first will be given here; our experience with the exercise test will be reported in a paper to follow this.

\* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania.

**Technique.** All patients were from the surgical wards of this hospital, and they were operated upon by members of the two surgical services. The cases for herniorrhaphy all had spinal anesthesia; in the other cases the anesthetic varied and will be mentioned later. The standard operative techniques were employed.

Our method of testing for abnormalities of the circulation by its response to arising has been described,<sup>10</sup> and a large experience with this test<sup>11</sup> formed the background for the present study. The standard procedure used was as follows.

No tests were done within 2 hours after a meal. The subject lay at rest for at least 15 minutes on the horizontal ballistocardiograph. Blood pressure was then taken and also the "H" (horizontal) ballistocardiogram. The subject then arose, walked about 3 paces to the vertical ballistocardiograph, and stood upon its platform. Three estimates of blood pressures were made at intervals of about 2 minutes. The "V" (vertical) ballistocardiogram was taken about 2 minutes after the upright position had been assumed, between estimates of blood pressure.

Cardiac outputs were calculated from the ballistocardiograms by the area method.<sup>9</sup> Normal standards for this test have been published.<sup>9</sup>

All patients with hernia to be repaired were tested in both positions before operation, usually on the day preceding it. On the sixth day after operation they were tested again, the ones who had not yet left their beds being tested in the horizontal position only. All were tested in both positions on the tenth day, the day the majority were first permitted out of bed, and again on the two days following. After this they were discharged. There were occasional deviations from this schedule due to difficulty in performing the tests on Sunday, so sometimes a day elapsed between two of the last three tests. A few estimations were lost by accident.

The patients subjected to more serious operations were tested on the same schedule as far as possible, but some of them were never able to stand, and many remained in the hospital for a much longer time and were studied at intervals during their stay.

Approximately 200 position tests were made in the entire investigation, and the results have been subjected to statistical analysis, the calculations being made by the methods of Fisher.<sup>2</sup> Whenever the word "significant" appears in this paper, it is used in the statistical sense, indicating a probability of less than 5 in 100 that chance would account for the result.

**Results.** As the patients with hernia were in good physiological health before operation, any changes which occurred after operation could be confidently attributed to postoperative convalescence. This was not the case in many other types of patients, for operation was often followed by improvement in their general condition which overweighed the changes due to convalescence. Therefore the data obtained after herniorrhaphy were studied first.

*Effect of Herniorrhaphy.* To analyze our results the values found before operation were subtracted from the corresponding values found after it, the difference representing the change caused by the procedure. These changes were averaged, and their means and the standard deviations about the means are recorded in Table 1. A statistical test was then applied, using Fisher's "t" function,<sup>2</sup> to ascertain whether the means were significantly different from zero (also see Table 1).

An example will make our method clear. The resting pulse rate before operation in patient A was 75. Six days after operation it was 70. The change following the operation is  $-5$ . The average of similar changes in all our 25 patients on the sixth day was  $+2$  (see

TABLE 1.—EFFECTS OF CONVALESCENCE FROM HERNIORRHAPHY ON THE CIRCULATION

Postoperative day of test	6th					10th					11th					12th				
	mean	$\sigma$	n	sig.	mean	$\sigma$	n	sig.	mean	$\sigma$	n	sig.	mean	$\sigma$	n	sig.	mean	$\sigma$	n	sig.
<i>Subjects lying at rest:</i>																				
Pulse rate per min. . . . .	0	15	25	no	+1	15	25	no	+1	12	25	no	+2	11	22	no	+2	11	22	no
Syst. B.P. mm. Hg . . . . .	+2	11	25	no	-5	11	25	yes	-8	10	25	yes	-6	11	23	yes	-6	11	23	yes
Diast. B.P. mm. Hg . . . . .	-2	12	25	no	-4	13	25	no	-7	12	25	no	-5	10	23	yes	-5	10	23	yes
Cardiac output per min./lb. . . . .	-13%	19%	24	yes	-8%	21%	25	no	-7%	20%	24	no	0	15%	23	no	0	15%	23	no
(average normal —100%)																				
<i>Subjects standing:</i>																				
Pulse rate per min. . . . .	+10	15	7	no	+9	13	22	yes	+5	10	24	yes	+5	15	22	no	+5	15	22	no
Syst. B.P. mm. Hg . . . . .	-12	14	7	no	-6	15	22	no	-6	12	24	yes	-8	12	22	yes	-8	12	22	yes
Diast. B.P. mm. Hg . . . . .	-5	11	7	no	-4	18	22	no	-3	11	25	no	-1	8	22	no	-1	8	22	no
Cardiac output per min./lb. . . . .	+14%	27%	5	no	+8%	30%	14	no	+10%	25%	21	no	+12%	24%	21	yes	+12%	24%	21	yes
<i>Differences between lying and standing values:</i>																				
Pulse rate per min. . . . .	+2	11	7	no	+8	11	22	yes	+4	9	24	no	+2	10	22	no	+2	10	22	no
Mean B.P. mm. Hg . . . . .	-4	5	7	no	+1	8	21	no	+2	9	25	no	+1	8	22	no	+1	8	22	no
Ratio { Cardiac output standing	+21%	40%	4	no	+16%	22%	16	yes	+15%	17%	21	yes	+10%	16%	20	yes	+10%	16%	20	yes
Cardiac output lying																				

The means are derived from differences between results found after and before operation. Thus the table shows that on the 10th day the systolic blood pressure averaged 5 mm. Hg lower than before operation.  $\sigma$  = standard deviation about the mean. n = number of cases studied. Yes or no = statistical significance for  $P=0.05$ .

Table 1). This value is not significantly different from zero. The scatter of the results can be seen from the standard deviation (also see Table 1).

The data in Table 1 under the subheading, "Differences Between Lying and Standing Values," were derived as follows: in subject A before operation the pulse rate when he was horizontal was 72. After he arose, it was 86. The change on arising was therefore +14 before operation. On the tenth day after operation the corresponding values were 73 and 94, the change on arising being +21. The difference due to the operation in this patient is  $21 - 14 = +7$ , and the average difference for all patients has been entered in Table 1. The data on blood pressure recorded in the lower one-third of Table 1 were derived the same way, but the changes in cardiac output on arising were calculated as ratios, and so the differences due to the operation are also expressed in per cent. The means and standard deviations in Table 1 have been rounded out to the nearest whole number.

Not all our data can be expressed in numbers and so entered in Table 1. Patients frequently had difficulty standing when they first arose from their beds. Some few could not stand at all, and many more stood but had so much tremor that the vertical ballistocardiogram was completely confused by it. This distortion of the record permitted a rough estimate of the amount of tremor, so a classification was made as follows: a perfect ballistocardiogram, *no tremor*; some distortion but not enough to prevent calculation of cardiac output at some place in the record, *slight tremor*; distortion so great that calculation of cardiac output is impossible, but systolic complexes can be identified sufficiently to count heart rate, *moderate tremor*; record completely confused by tremor, not even the heart rate can be counted, *marked tremor*.

To avoid unconscious bias, the records were arranged in a random order and presented to the senior author without anything to identify them. The results of his classification of the amount of tremor shown are given in Table 2. Obviously tremor in the upright position increases greatly after operation, but the abnormality largely disappears soon after the patients are up and about.

*Effect of Exercise and Early Rising.* Ten of the patients operated upon for hernia were treated differently from the others. Beginning with the second postoperative day these patients were placed on the following program which was carried out under the direction of a nurse each morning and again each afternoon for the duration of their stay in the hospital: for 5 minutes, while lying on their backs, they alternately flexed and extended first the wrists, then the elbows, then the shoulders in each of 3 directions, then the ankles, and finally the knees and hips together. Each joint in turn was flexed about 10 times in 20 seconds so that the series was repeated about 3 times in the 5 minutes allowed. The patients then stood beside their beds for 5 minutes and often walked a few steps. Then, after returning to bed, they repeated the exercises for 5 minutes.

The control group, following the usual hospital routine, took no

exercise and stayed in bed until the tenth day after the operation. Patients of both groups were tested on the sixth, tenth, eleventh, and twelfth days after operation.

To measure the effect of the exercise and early rising the subjects were arranged into pairs. For each exercised patient a mate was chosen from the unexercised group of the same sex and as near the same age as possible. All were males, and the ages of the 10 pairs were as follows: 45 and 46, 28 and 29, 33 and 31, 17 and 17, 21 and 18, 60 and 68, 37 and 29, 60 and 70, 26 and 24, 42 and 28.

The effect of the exercise on pulse rate, blood pressure, and cardiac output was estimated as follows: the change due to the operation was calculated for each patient by subtracting the value found before it. This value for the unexercised subject was subtracted from the corresponding value found for his exercised mate. The resulting difference, due to the exercise, was found for each pair, and an average for the 10 pairs was calculated. Finally a statistical calculation was made to determine whether this average was significantly different from zero.

An example will make the process clear. We have paired our patients, A and B; C and D, etc. A and C have been exercised, B and D not. The resting pulse rates before and 10 days after operation were for A, 80 and 84; for B, 75 and 78; for C, 65 and 64; for D, 73 and 76 per minute. The differences due to the operation were therefore +4, +3; and -1, +3. Now subtracting this value found in the unexercised B and D from that of their exercised mates, we have differences of +1 and -4 which may be attributed to the exercise. The average of these figures is -1.5. The average of our 10 pairs was -1.6, and by statistical methods we determine whether this value is significantly different from zero. A calculation similar to this was done on the measurements of pulse rate, blood pressure, and cardiac output made on each of the 4 days of the tests.

We will not report these results in detail because they were so largely negative. Nothing significant could be attributed to the exercise except on the tenth day after operation. On this day 3 of the unexercised patients were unable to stand, and 5 more had marked tremor, whereas all of the exercised patients could stand and only 1 had a moderate tremor. Tested by the method of  $\chi^2$  this difference is highly significant. In addition, the standing systolic blood pressure taken on the tenth day after operation averaged 13.4 mm. of Hg lower in the exercised group, and this was also significant. While the meaning of this blood pressure difference is not clear to us, we can conclude from the difference in tremor and ability to stand that the exercised patients were in better condition on this day. However, both significant differences disappeared by the day following, and we could find no other significant differences which could be attributed to the exercise in pulse rate, blood pressure, or cardiac output in either the horizontal or standing positions on any other day. This similarity of result is the justification for including both the exercised and the unexercised patients in same statistical analysis recorded in Table 1.



*Results in Patients Convalescent from More Serious Operations.* We studied 19 patients subjected to the following operative procedures: 3, exploratory laparotomy with nothing else done; 3, cholecystectomy; 3, colostomy, 2 for carcinoma, 1 for lymphopathia venereum; 1, lower esophagectomy for carcinoma; 3, gastric resection, 2 for carcinoma, 1 for ulcer; 1, gastrostomy for carcinoma of the esophagus; 3, craniotomy for tumor, for hematoma, and for exploration; 1, laparotomy for intestinal obstruction; 1, repair of mycotic subclavian arteriovenous aneurysm.

The anesthetics used also varied in the different patients: spinal, local, cyclopropane, nitrous oxide and oxygen, often with the addition of ether were employed. Postoperative complications such as fever occurred in some but not others. Treatment varied greatly, some patients receiving large amounts of fluids intravenously at operation and in the days following it, while others received none. Obviously the patients had so little in common that a study of the averages of our results would be meaningless. However, in most cases the trend of the results resembled those found after herniorrhaphy except where 1 of 2 factors entered into the situation.

Deviation from the usual postoperative pattern could often be attributed to the administration of large amounts of fluid given intravenously. This prevented the usual postoperative fall of cardiac output, and sometimes replaced it with a rise. Thus N. S., who had a gastric resection for carcinoma, received 13.5 liters of blood, and glucose, saline, or gelatin solutions intravenously within the week after operation. His resting cardiac output, + 4% above average

#### LEGEND FOR FIG. 1.

Fig. 1.—Ballistocardiograms obtained in the horizontal position before and after operation. The time record on the top applies to all the records; its largest interval equals one second. The reproduction is actual size. A—L. A., age 26, 5 feet 8 inches, weight 146 pounds, a healthy person except for an inguinal hernia. Record obtained the day before operation. The calculated cardiac output did not deviate from average normal. The empirical normal limits are  $\pm 22\%$ . B—Same subject on the sixth day after operation. The cardiac output is calculated to be  $-30\%$ , a subnormal value. C—Same subject eleven days after operation. Cardiac output  $-4\%$ . D—R. S., age 35, 5 feet, 75 pounds. Extremely emaciated from carcinoma of the pharynx. *First record* day before operation. Cardiac output  $-17\%$  if calculated as the basis of her ideal weight, 118 pounds. *Second record*, nineteenth day after gastrostomy, cardiac output  $+22\%$ . E—W. L., age 70, 5 feet 4 inches, 140 pounds. *First record* day before inguinal herniorrhaphy cardiac output  $-12\%$ . *Second record* six days after operation is abnormal in form, the I wave being widened and shallow, approaching the segment of a circle in shape in contrast to the normal deep triangle. In the last complex shown the J wave is flattened and notched. Cardiac output cannot be estimated from such records. In records obtained on the tenth, eleventh, and twelfth day the ballistic form had returned to normal. F—H. J., age 66, 5 feet 8 inches, 111 pounds. *First record* day before exploratory laparotomy, cardiac output  $-19\%$  referred to his ideal weight. Abdominal carcinomatosis found at operation, biopsy performed. *Second record* six days after operation. The form of most impacts is abnormal, the J waves being reduced in amplitude, notched or flattened. The form varies markedly from beat to beat. An occasional normal complex is seen. *Third record* 8 days after operation. The amplitude is larger, but the abnormalities in form remain the same. The patient died six days later. Necropsy found carcinomatosis, intestinal perforation and peritonitis. The heart weighed 300 grams. The muscle was firm, the chambers slightly dilated. The coronaries were patent although they contained sclerotic plaques. The valves were normal.

normal before operation, was + 22% above on the first test 11 days after it. After the extra fluid was stopped the circulation diminished to its original level. G. H., whose arteriovenous aneurysm was repaired,

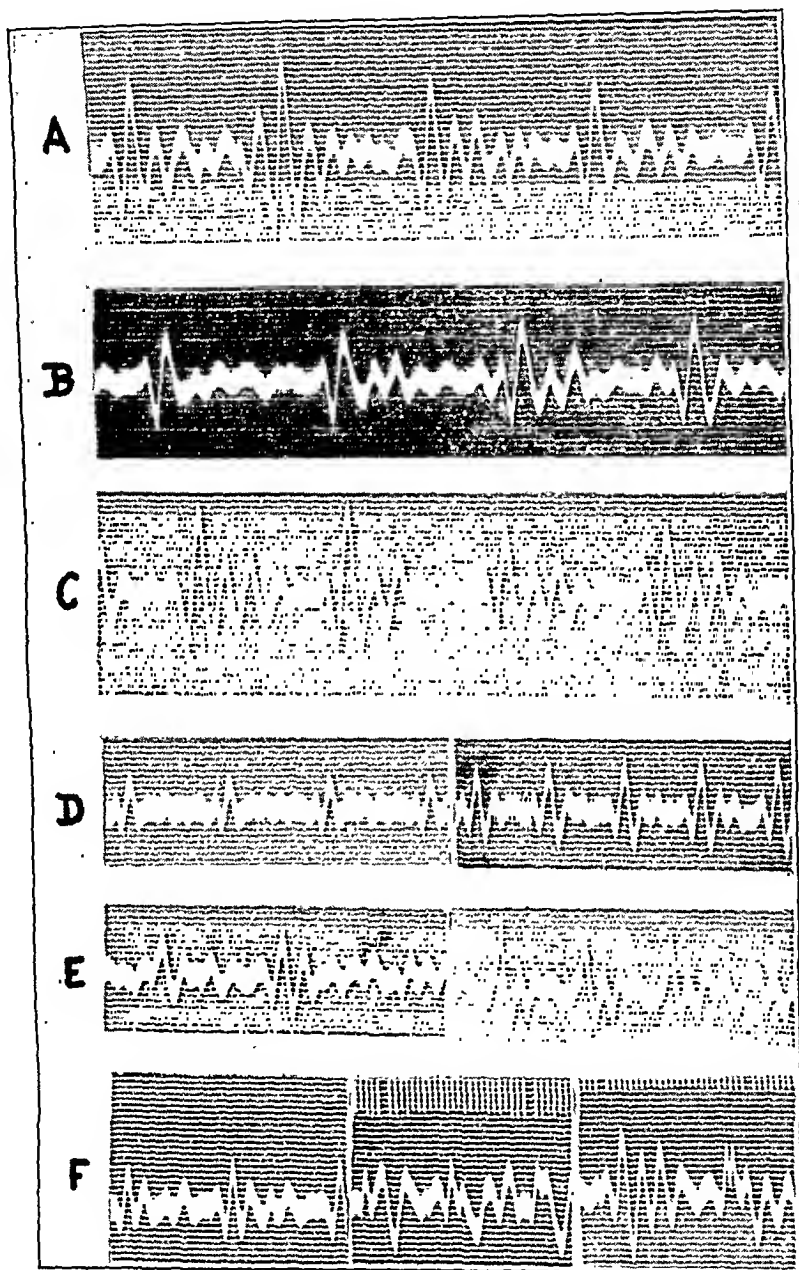


FIG. 1

received 5.1 liters intravenously at operation and during the day following. Her cardiac output, + 9% before operation, was + 39% on the second day after it, and gradually returned to the original level. M. H., who had a colostomy for lymphopathia venereum

received a total of 9650 cc. during the first 3 postoperative days. Her resting cardiac output tested on the sixth day after operation was the same as it had been before operation.

When the patient's ability to take food and fluids was improved by the operation, the postoperative course differed from the usual. Thus R. S., aged 35, and 44 pounds under her ideal weight, as a result of carcinoma of the pharynx, had a pulse rate of 83 and a blood pressure of 95/70 before operation. At this time her resting cardiac output per minute was in the normal range, 17% below average normal, if referred to her ideal weight. After gastrostomy permitted better feeding, the pulse rate rose to 118, the cardiac output increased to +17% and the blood pressure to 108/84. These records are shown in Figure 1. In 7 tests made at intervals during the next month the pulse rate and cardiac output remained at their high postoperative level, but the blood pressure diminished slowly until the preoperative value was regained. A similar result was obtained in S. B., aged 52, who had a colostomy for carcinoma. The resting cardiac output before operation was subnormal, -26%; after operation permitted more normal gastrointestinal function, it rose to -4% and remained within normal limits in the 5 tests made thereafter.

Three of our patients died. L. O., aged 51, died suddenly 18 days after the removal of a carcinoma of the lower end of the esophagus. After operation she was never able to stand or even to sit in bed without becoming dizzy and faint, these symptoms being accompanied by marked fall of blood pressure. Necropsy showed that death was due to a large pulmonary embolus.

H. J., aged 66, died 14 days after an operation for intestinal obstruction due to carcinoma. His blood pressure was 142/78 before operation and rose slowly to 164/90 after it. The chief interest in this case was in the change in form of the horizontal ballistocardiogram (Fig. 1). Normal before operation, it became increasingly abnormal after it, so cardiac dysfunction should be thought of as a factor in the terminal picture.

R. S. with carcinoma of the pharynx died suddenly of a rupture of an involved carotid artery 82 days after operation. The interest in this case has been mentioned.

**Discussion.** On the basis of the significant results one may draw a picture of the changes in the circulation which may be expected as a result of surgical operations and the bed rest which follows them.

When observations are made on patients in the *horizontal position*, cardiac output per minute is found to be significantly diminished for several days after operation, but it then slowly increases and by the day of discharge has returned to the preoperative level. The resting systolic blood pressure, unchanged for a short period after operation, becomes significantly diminished later, to rise somewhat before discharge. The resting diastolic blood pressure behaves quite similarly, but in our data the average remained significantly diminished to the end of our tests. The resting pulse rate is unchanged after operation. All these blood pressure and pulse rate changes are small, and none

of them would have attracted the attention of attending physicians employing the usual methods of examination.

When observed with the patient in the *vertical position*, the changes found after operation are more striking. Some patients cannot stand without fainting; others stand only with marked tremor which doubtless aids in supporting their circulation. The standing pulse rate averages 10 beats per minute faster when patients are first allowed to stand than before operation. This abnormality rapidly diminishes as the patient begins to be up and about the ward. Standing systolic blood pressure is lower after operation, but diastolic blood pressure remains unchanged. Standing cardiac output per minute is calculated to be higher after operation but was only significantly so in the last day of our tests.

Other abnormalities of convalescence can be demonstrated by studying the changes which occur when the subject arises. In normal persons the pulse rate always accelerates on arising, the average increase being 17 to 18 per minute.<sup>7,10</sup> In our patients, on the tenth day after operation, the day most of them left their beds for the first time, the pulse rate on arising increased on the average of 7.6 per minute more than it had before operation. On this same day the calculated cardiac output also increased more on arising than it had before operation, and this difference was significant. All these abnormalities disappeared within 3 days after the subject was up and about.

This picture of circulatory abnormalities in convalescence, drawn from our results on the patients operated upon for hernia, can be extended to those subjected to more serious operations with certain modifications. The more seriously ill patients often exhibited abnormalities of the circulation in the upright position before operation, and these were greatly increased after it, so that some patients were unable to stand without marked tremor and a greatly accelerated pulse rate for many weeks. In general, the abnormalities found after severe operations were identical with those recorded in Table 1 if they were not modified by 1 of 2 factors. First, the administration of large amounts of fluid after operation increased the cardiac output or prevented its diminution, an effect probably comparable to those found by Hardy and Godfrey,<sup>4</sup> and Fletcher, Hardy, Riegel and Koop<sup>3</sup> after the intravenous administration of saline solution and gelatin to dehydrated patients. Second, if the operation permitted better nourishment of the patient, the postoperative findings showed a picture strikingly different from that found before operation.

Abnormalities of ballistic form appearing for the first time after operation have been encountered twice in this study. One of these patients died; in the others the ballistic form returned to normal before discharge. Other instances of transient abnormality of ballistic form after operation have been published.<sup>12</sup> Thus we have evidence that operation can effect the heart adversely. However, such an effect is rare. In our experience it has occurred only in persons over 65 or in those with heart disease manifest before operation.

Certain of our results are consistent with those of other investigators

studying related problems; and as the whole field of convalescence has been recently reviewed,<sup>14</sup> the number of references needed here is small. Snyder<sup>8</sup> found a marked reduction of resting cardiac output in 4 of 7 patients tested on the first day after operation with recovery by the time of discharge. Our results are similar although our patients were first tested on the sixth day. Since certain of our cases receiving large amounts of fluid intravenously did not show this abnormality, one wonders whether reduction of blood and tissue fluid volume from hemorrhage, capillary leakage, sweating and the like, accompanied by low fluid intake were not the cause.

Most persons who have had an operation can testify to the difficulties and symptoms which beset them when they first arose from bed. We have found no previous study of the blood pressure and pulse rate on assuming the vertical position during postoperative convalescence, but similar abnormalities were found during convalescence from fever by Kopp.<sup>6</sup> The abnormalities of our convalescents when they first arose from bed do not differ from those found in many persons sick from a large variety of causes,<sup>11</sup> and especially in certain cases of neuro-circulatory asthenia.<sup>13</sup> Inability of the peripheral circulation to adjust quickly to the additional demands put upon it by the upright position, with resulting cerebral anemia, is the explanation usually given and with this we concur, although the fact that the cardiac impacts were often large inclines us against the view that diminished cardiac output from a diminished venous return plays a part in the symptoms of such as these. That this mechanism may cause syncope under certain other conditions is not disputed.

Whatever may be the exact physiological abnormality which prevents proper adaptation to the standing position after operation, it is improved by practice. It took only a day or two of being up and about for the response to arising to return to normal in most cases. On the tenth day after operation those exercised and permitted out of bed from the second day onward were clearly more normal in this respect than those who had remained in bed until the tenth day.

Many of the abnormalities found in our patients after operation are similar to those demonstrated in healthy persons who have volunteered to remain in bed.<sup>1,5</sup> However, in the latter case the abnormalities usually developed after a much more prolonged bed rest than our patients had; and while we do not doubt that bed rest was a factor in our results, we believe that the operation itself played the larger part.

During the investigation we often asked ourselves whether the changes found after operation could be due, not to effects of the operation itself, but to apprehension of it, the emotional effect altering the circulation before operation and causing a change by passing off when the operation was over. The possession of normal standards for our test<sup>11</sup> aided in the identification of persons with severe emotional disturbances before operation. Inspection of Tables 1 and 2 show that the resting cardiac output, standing pulse rate and tremor, after changing from the preoperation level, returned to it again before discharge, so there seems no possibility that emotion could account for

these results. However, when the original level was not regained during the period of observation, as was the case with systolic pressure, the possibility that such an emotional effect entered into the result cannot be excluded.

TABLE 2.—TREMOR WHEN STANDING UPRIGHT BEFORE AND AFTER HERNIORRHAPHY IN 25 CASES

	Before operation	After operation		
		10th day	11th day	12th day
Unable to stand . . . .	0	2	0	0
Marked tremor . . . .	0	4	0	0
Moderate tremor . . . .	2	3	6	1
Slight tremor . . . .	15	13	12	16
No tremor . . . .	7	3	7	6
Not tested . . . .	1	0	0	2

The numbers given represent the number of patients in each category.

Our data permit an objective evaluation of the program of exercises in bed and early rising from bed that we tried. We obtained no evidence whatever that the exercised group was in anyway harmed by the more novel routine. Also, on the tenth day when the group in the regular routine was first allowed out of bed, the performance of the exercised patients was definitely superior. But it took only 1 day of being up and about for the group on the regular routine to equal the performance of those on the program of exercises and early rising, so we doubt whether anything very important was gained. The demonstration had the result of altering the routine handling of patients with hernia in the Hospital of the University of Pennsylvania, and many of them are now permitted out of bed on the third day after operation and sent home much sooner than had previously been the case.

The data obtained in this investigation permits conclusions about the objective detection of the convalescent state and, therefore, about methods for passing judgment on procedures designed to shorten convalescence. In this study we have had the great advantage of possessing data on our patients before they became convalescent. If one first saw the patient during convalescence, judgment of his state would be far more difficult.

For example, one of the most significant abnormalities we discovered is the change in pulse rate which occurs on arising. In healthy persons the average pulse rate increases 16.6 per minute when they arise;<sup>10</sup> on the tenth day of convalescence the increase is almost 50% greater than this. For healthy persons the usually accepted normal range, twice the standard deviation applied to both sides of the mean, extends from 0 to 33 per minute; that is, any person whose pulse rate on arising increases by any amount between 0 to 33 per minute would have to be regarded as normal.

A physician seeing the patient for the first time after operation would have data such as this on which to base his judgment, and, after ascertaining the lying and standing pulse rates in convalescents, he could use it. However, judging from our data obtained after hernior-

rhaphy he would detect an abnormality in only 22% of his cases. After more serious operations this percentage would be higher, but, obviously, the test is too crude to permit final judgment on the fitness of any person. It might be of some service as a first screening test, those failing being judged unfit, while those passing were considered well enough to take a more strenuous exercise test. A study of all our data on pulse rate, blood pressure, and cardiac output does not disclose any more promising basis for designing a satisfactory test for the presence, and so the duration, of convalescence in an individual first seen after operation.

When one is comparing two series of cases, however, a statistical analysis of tremor, blood pressure, pulse rate, and ballistocardiographic changes yields results on which conclusions can be based with confidence. The number of cases needed will depend, of course, on the size of the abnormality they develop, but some hints for future studies of convalescence can be obtained from our data. It is to be noted (Table 1) that only 7 of our subjects were tested while standing on the sixth postoperative day. The abnormalities found in these subjects were larger than on any other day, but their number was so small that statistical significance was not attained. With 20 or more subjects much smaller abnormalities were found significant. Series of this size should be sufficient and would permit detection of the objective manifestations of convalescence and so aid in the evaluation of methods designed to shorten it.

**Summary.** Forty-four patients have been studied before and repeatedly after surgical operations. The test used consisted of estimates of pulse rate, blood pressure, and cardiac output (ballistocardiogram) under standard conditions in both the horizontal and vertical positions. The results have been subjected to statistical analysis.

The average of results obtained in 25 cases operated upon for hernia disclosed that the following significant changes occurred during postoperative convalescence:

In the *horizontal position*, cardiac output was diminished soon after operation, and blood pressure was diminished later. In the *vertical position* pulse rate was increased, cardiac output tended to be increased and systolic blood pressure to be diminished.

The difference between the lying and standing pulse rates, and the ratio between lying and standing cardiac outputs increased after operation. There was more tremor on standing, and occasionally subjects were unable to remain standing after operation.

After more serious operations the changes found in convalescence were generally similar to those described after herniorrhaphy with two exceptions. (1) The administration of large amounts of fluid by vein prevented the postoperative fall of cardiac output or caused it to increase. (2) If the operation permitted better nutrition of the patient, improvement from this cause far overbalanced the effects of the operation *per se*.

The scatter of the data was great enough to prevent the development of a simple test for the duration of convalescence which could

be applied to single individuals. Nevertheless significant comparisons could easily be made between small series of cases.

Ten cases of hernia were given a program of exercises in bed and early rising beginning with the second or third day after operation. Comparison with a group not so treated showed that the exercised group tolerated the upright position better than the controls when the latter were first allowed out of bed. This advantage lasted only for a day, however, so we doubt whether anything important was gained by the exercise program.

#### REFERENCES

1. BARR, D. P.: Personal communication.
2. FISHER, R. A.: Statistical Methods for Research Workers, 7th ed., London, Oliver and Boyd, 1938.
3. FLETCHER, A. G., HARDY, J. D., RIEGEL, C., and KOOP, C. E., J. Clin. Invest., 24, 405, 1945.
4. HARDY, J. D. and GODFREY, L., JR., J. Am. Med. Assn., 126, 23, 1944.
5. KEYS, A.: Personal communication.
6. KOPP, I.: Am. Heart J., 18, 46, 1929.
7. SCHNIEDER, E. C.: Physiology of Muscular Activity, 2nd ed., Philadelphia, Saunders, 1941.
8. SNYDER, J. C.: J. Clin. Invest., 17, 571, 1938.
9. STARR, I. and SCHROEDER, H. A., J. Clin. Invest., 19, 437, 1940.
10. STARR, I. and RAWSON, A. J., Am. J. Physiol., 134, 403, 1941.
11. STARR, I.: J. Clin. Invest., 22, 813, 1943.
12. STARR, I.: AM. J. MED. SCI., 202, 469, 1941.
13. STARR, I.: AM. J. MED. SCI., 204, 573, 1942.
14. Symposium on Physiological Aspects of Convalescence and Rehabilitation, Federation Proc., 3, 188, 1944.

## CONVALESCENCE FROM SURGICAL PROCEDURES

### II. STUDIES OF VARIOUS PHYSIOLOGICAL RESPONSES TO A MILD EXERCISE TEST

BY ISAAC STARR, M.D.

ROBERT L. MAYOCK, M.D.

AND

MARJORIE G. BATTLES

PHILADELPHIA, PENNSYLVANIA.

(From the Hartzell Research Department of Therapeutics; The Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania; and The Surgical Clinic of the Hospital of the University of Pennsylvania)

THE aim of this investigation was to explore the possibilities of finding objective methods of demonstrating abnormalities present in convalescence after surgical procedures which would serve as an indication of the duration of the convalescent state and as a test of measures designed to shorten it.

It was our belief that no abnormalities characteristic of convalescence would be demonstrable while the patients lay at rest, but we hoped that when they performed a task, abnormalities might manifest themselves. The first task assigned was the maintenance of the upright

\* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania.



position, and our experience with that test has been described in the previous communication.<sup>11</sup> In this paper we will describe our experience with a mild exercise test which could be applied to persons in bed.

The number of exercise tests in the literature is large,<sup>9</sup> but none of them seemed to meet our requirements. First, we needed a test which could be performed without danger of rupturing an unhealed abdominal incision. Second, to make the test generally useful we needed to limit ourselves to apparatus in common use in hospitals and to techniques which did not require unusual skill and training of the operating personnel. For the first reason, tests, such as stair climbing or riding the bicycle ergometer, were regarded as unsuitable for patients immediately after operation; and, for the second reason, we sought to avoid the apparatus and technique usually required for gas analysis. So we finally designed an easy weight lifting test which could be performed by the subject while lying in bed on his back and breathing from a spirometer designed to measure basal metabolic rate. By this means oxygen consumption could be determined without gas analysis and both rate and volume of respiration estimated from the spirometer record as well. We also counted pulse rate and in a few experiments took ballistocardiograms.

Estimations made during the exercise failed to demonstrate any significant abnormalities which could be attributed to the convalescent state, but observations made after the exercise was over demonstrated that the return to normal was significantly slower during convalescence.

**Methods. Subjects.** Five healthy persons were studied, the authors and two persons associated with other phases of the project.

The patients studied all came from the Surgical Clinic of this hospital. The operations were performed by members of the services of Dr. E. L. Eliason or Dr. I. S. Ravdin. A satisfactory study was completed on 20 patients of whom 12 were operated upon under spinal anesthesia for hernia. In the others, the operations performed were gastric resection in 3 cases; cholecystectomy in 2; appendectomy, choledochostomy, and intestinal resection for carcinoma in 1 each. All made satisfactory recoveries from the operative procedures.

**Schedule.** Every patient was tested before operation, and most of them several times afterward. The relation between the day of operation and the day of test varied somewhat more than in the previous study. Most patients were tested on the third or fourth day after operation, again on the ninth or tenth day, and finally about the seventeenth day if they still remained in the hospital. In all, 91 exercise tests were performed.

**Exercise Tests.** No test was made within 2 hours after a meal. The patient lay on his back either in bed or on the horizontal ballistocardiograph. A half face mask with a pneumatic cushion was held over nose and mouth by straps around the head, and its outlet was attached to a Benedict-Roth basal metabolism spirometer with a capacity of 5 liters, having valves and not a motor blower. The spirometer was filled with oxygen.

After a rest period of about 15 minutes the oxygen consumption was recorded for 4 to 6 minutes. Then, if the record was satisfactory, the subject was given a 10 pound iron bar, and a metronome was started ticking every second. With each tick the subject alternately raised and lowered the weight from his chest to arm's length above it. He thus raised it 30 times in a minute while continuing to breathe from the spirometer. After exercising thus for 1 minute, the exercise was stopped. The record of oxygen consumption was continued for the next 5 minutes or until the slope of the record became linear. Such a record is shown in Figure 1.

Oxygen utilization during the exercise was calculated as follows. After inspection of the record obtained before the exercise was started, a line was drawn as in the routine estimation of basal metabolic rate. This line is labeled 1 in Figure 1. During exercise the record sometimes moved erratically, and its form varied greatly from subject to subject. So in some cases this part of the record could not be used as basis for a line. However, within a few minutes after exercise had ceased, the record became linear once more so that a second line could be drawn. This line is labeled 2 in Figure 1. This second line was, as a rule, nearly parallel with the first line, but it was not a continuation of the first line. If extrapolated to the right, the second line lay above the first because of the extra oxygen consumed during and immediately after the exercise. To estimate this extra oxygen the adjacent ends of lines 1 and 2 were joined by a third line (line 3, Fig. 1) drawn regardless of the record. This third line extended over the record obtained during the minute of exercise and over the period after it during which the oxygen debt was being paid. It is labeled 3 in Figure 1.

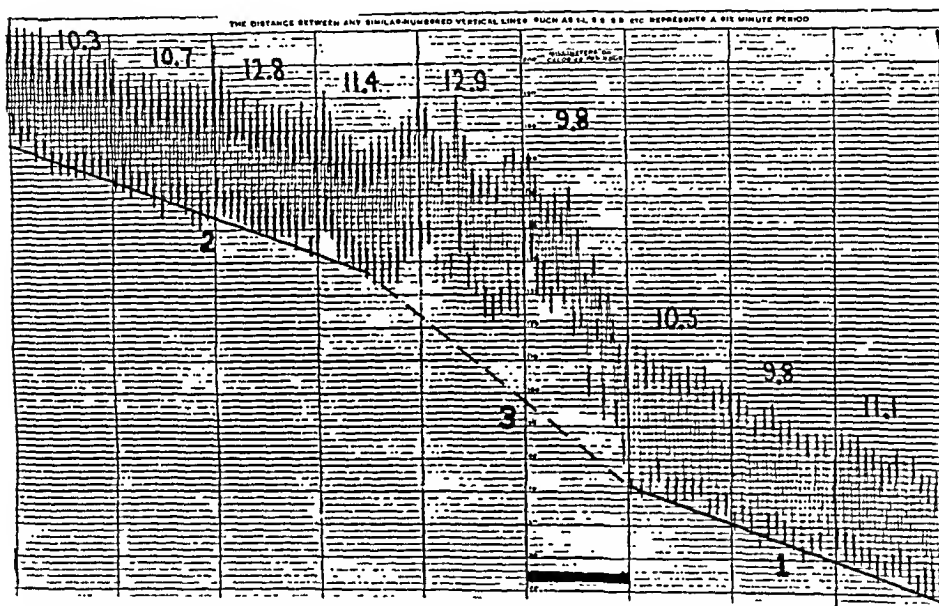


FIG. 1.—Record obtained on Patient G. F. (age 30, height 5 feet 5 inches, weight 138 pounds) with a Benedict-Roth metabolism spirometer before and after exercise on the 14th day after operation. Read from right to left. The bar shows the duration of the exercise (1 minute). The numbers beneath the record refer to the lines drawn to estimate oxygen consumption. The numbers above the record are the respiration in liters per minute. The record ran for a longer period both before and after exercise than is shown in the illustration.

In certain records there was some doubt where the junction of lines 2 and 3 should be placed. However, since lines 1 and 2 were usually parallel or nearly so, the position selected for this junction made little or no difference to our calculations of the oxygen required for the exercise.

From these 3 lines the extra oxygen needed for the exercise was calculated. By the usual methods used for estimating metabolic rates, we estimated oxygen consumption in terms of dry gas under standard conditions and applied the results to our problem as in the following example:

From the data given in Figure 1 we calculate:

1. Oxygen consumption before exercise (from line 1) = 208 cc. per minute.
2. Oxygen consumption when, after exercise, the record has become linear (from line 2) = 213 cc. per minute.

3. Average oxygen consumption over the two and one-half minute period of exercise and recovery (from line 3) = 480 cc. per minute.

We may interpret this data as follows:

1. Oxygen consumption at rest: 208 cc. per minute.
2. Oxygen consumption during exercise: 480 cc. per minute.
3. Extra oxygen consumption needed for exercise:  $480 - 208 = 272$  cc. per minute.
4. Duration of exercise and recovery period 2.5 minutes.
5. Total extra oxygen used for exercise  $272 \times 2.5 = 680$  cc.

We naturally had most confidence in the result when lines 1 and 2 were parallel or nearly so. In some cases, however, these lines diverged, and then it was hard to be certain how best to handle the data. There were two possible methods. The resting oxygen consumption could be calculated from the average of the values found before and after exercise, obtained from lines 1 and 2. This was usually satisfactory enough, but occasionally we obtained the surprising result that no measurable oxygen was used in the exercise, a phenomenon which does happen in certain diving animals and in the sloth.<sup>6,7</sup> However, when the resting oxygen consumption was calculated from line 1 only, this result was obtained only twice; so we came to prefer this method, and it is used in the example given above.

Occasionally we were left in doubt whether the oxygen debt had been fully paid by the end of the test. In some such cases we often prolonged the record by refilling the spirometer with oxygen, but, nevertheless, complete return to the pre-exercise level did not always take place during the period of observation. In such a case we finally decided to add the extra oxygen consumed in a standard period, the first 5 minutes of line 2, Figure 1, to that consumed during the exercise and the recovery period which immediately followed it. In these cases the calculation was made as follows:

1. Oxygen consumption before exercise = 230 cc. per minute.
2. Oxygen consumption during exercise and immediate recovery period (2 minute duration) = 420 cc. per minute.
3. Oxygen consumption for next 5 minute period = 240 cc. per minute.
4. Extra oxygen for exercise period,  $(420 - 230) \times 2 = 380$  cc.
5. Extra oxygen for next 5 minutes  $(240 - 230) \times 5 = 50$  cc.
6. Total oxygen used in exercise = 430 cc.

We are by no means certain that this is the best way to handle the data, for it is possible that the exercise changed the resting metabolic rate of our subjects by arousing them and so introduced an error into our results when calculated by this method.

In short, while there seemed no perfectly satisfactory method of making the estimation from some of our records, the errors involved were probably small. We tried several methods of making the calculation and found they made no material difference to the conclusions that could be drawn from our data.

The duration of increased oxygen consumption after exercise was measured from the end of the exercise period to the resumption of the resting metabolic rate at the junction of lines 2 and 3. This duration was often not easy to measure with great accuracy, and we were content to estimate it to the nearest  $\frac{1}{2}$  minute. Change in the mid-position of the diaphragm during exercise, as is shown by the record in Figure 1, increased the difficulty of the measurement, but this complication occurred in very few cases.

*Respiration* was estimated by measuring the up-strokes on the record and applying the calibration of the spirometer. The figures given in the tables represent the volume as measured over water in the spirometer. The temperature of gas in the spirometer was always recorded, and the median value was  $25^{\circ}$  C. In the series of tests done on any individual the range of the spirometer temperatures was so small that we have not corrected the data for it. The extra volume of respiration induced by the exercise was calculated in a manner similar to that used for extra oxygen, as follows:

In the record shown in Figure 1 we find:

1. Respiration before exercise, average of 3 minutes = 10.5 liters per minute.

2. Respiration during exercise and recovery period, average of 4 minutes = 11.7 liters per minute.

3. Respiration during last 2 minutes = 10.5 liters per minute.

4. Extra respiration needed for exercise  $4 (11.7 - 10.5) = 4.8$  liters.

As the respirations after exercise often varied from minute to minute, it was difficult to determine the exact time at which the pre-exercise level was regained. Hunt and Dufton<sup>5</sup> had the same experience, so following their example we calculated a "dyspnea ratio" as follows. Respiration during the exercise and for the first minute after it was neglected. The volume of respiration for the second, third, and fourth minute after exercise was taken and divided by the volume for the 3 minutes which preceded the exercise. Statistics for this quotient are entered in Table 6. Our quotient differs from that of Hunt and Dufton<sup>5</sup> as they measured respiration for one minute longer than we. After the much more vigorous work test they employed, this was doubtless advantageous, but inspection of our data suggested that the increased breathing was often over by the fourth minute after the mild exercise we employed.

*Ballistocardiograms*<sup>10</sup> were made before and after the exercise in some, but not in all subjects. During the exercise impacts from the patients' movements destroyed the record of the cardiac impacts, so estimations of cardiac output during exercise were not possible. We obtained satisfactory records within a few seconds after exercise was over. Therefore, the record was started when exercise was stopped and let run for about a minute. Another record was taken 5 minutes later.

Inspection of the records obtained in the first cases showed so little that could be attributed to convalescence that ballistocardiograms were omitted from the latter part of the study. This simplification permitted us to apply the exercise test to patients without moving them from the ward.

*Pulse rate* before and after exercise was counted from the ballistocardiogram or taken at the wrist.

*Statistical Calculations.* The methods of Fisher<sup>4</sup> were followed. Whenever the word significant is used in this paper, it is used in the statistical sense of indicating that the probability that chance would account for the result was less than 5 in 100. Thus, when the word "significant" is used, the reader should realize that a calculation to determine it was made, although the calculation itself may not be mentioned.

**Results.** To gain experience with the test we first used it 12 times on 5 healthy persons (Table 1). From the averages (Fig. 2) it is apparent that, as one would expect, the exercise was followed by increased oxygen consumption, respiratory volume, cardiac output, and heart rate. The effect on respiratory rate varied; subject L. S., who had been a sprinter in his youth, once held his breath for a large part of the exercise period. In many experiments the oxygen debt was so small that its payment after exercise could not be detected. In some cases this was obviously due to an artefact, for changes in the mid-position of the diaphragm during exercise made it impossible to decide how much oxygen was consumed and how much merely taken into the lungs in any given minute. Thus, records similar to Figure 1 would lead to an overestimation of oxygen consumption during the minute of exercise and an underestimation during the recovery period; but, as the diaphragm eventually returned to its former position, the total oxygen consumed during the exercise and recovery period can be estimated accurately. However, in most records the mid-position of the diaphragm did not change, and the minute to minute oxygen consumption could be measured with reasonable confidence.

TABLE 1.—EFFECT OF A STANDARD EXERCISE TEST ON NORMAL SUBJECTS

TABLE 1.—EFFECT OF A STANDARD EXERCISE TEST ON NORMAL SUBJECTS															
Circulation															
Name Sex Age ht. wt.	Date	Respiration					Cardiac output (deviation from average normal, %)					Pulse rate (per minute)			
		Volume (liters per minute)					Rate (per minute)					Immed. after			
		Before		During		After		Before		Immed. after		Before	5 min. after		

Inspection of the results obtained on the same person on different days (Table 1) shows a high degree of variation. On September 20, R. M. apparently performed the test without using any extra oxygen from the spirometer; one notes that before exercise on this day his resting respiration and oxygen consumption were larger than in any other test. The effect of the exercise on cardiac output was also variable; on September 20, we demonstrated no increase in cardiac

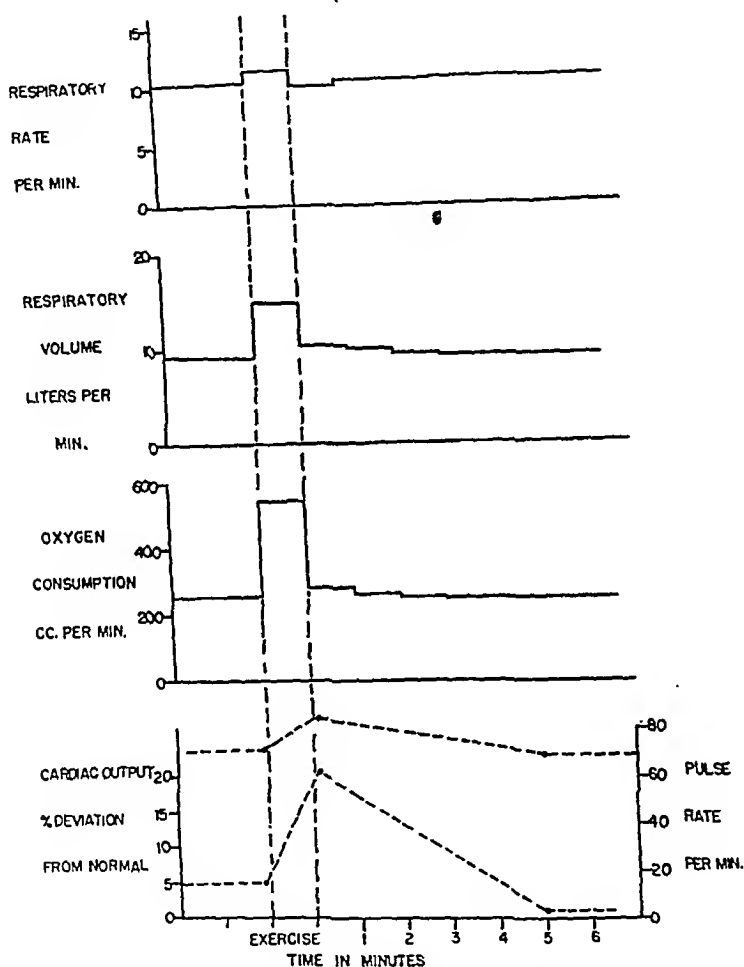


FIG. 2.—Average of the results obtained before, during and after exercise in 5 normal subjects who performed a weight-lifting test of approximately 600 foot-pounds for 1 minute.

output after exercise in L. S.; on September 15, I. S. showed a delayed effect. Such variations warned us that it would be difficult to draw significant conclusions from the results, but at this stage in the investigation it was conceivable that the effect of the surgical procedure would be great enough to outweigh the inherent variability of the responses to exercise.

The averages of our results on respiration and oxygen consumption after work are in agreement with expectations based on other

studies.<sup>1,2,3,9,12</sup> The work performed by our healthy subjects was much less than in most similar studies and their respiration and oxygen consumption were proportionally less also, so that the average ratio between work performed and oxygen consumption was essentially similar to that reported by other authors.

Using the usual method of calculation, the mechanical work performed by our subjects was approximately 600 foot-pounds per minute. The average oxygen required for the performance of this work by our normal subjects was 318 cc. Converting both work and oxygen to calories in the usual manner,<sup>13</sup> the average mechanical efficiency of our healthy subjects was 12.7%, a value close to that found in other weight-lifting tests.

When we tested *patients*, distortion of the results by emotion occurred frequently. This was manifest by the abnormally large resting oxygen consumption, and in 9 patients this finding forced us to abandon the test. Occasionally a patient who had performed in a satisfactory manner before operation was excited at a later test. In the tests whose results we accepted, the resting metabolism was always within or very near the normal basal range although we were not working under strictly basal conditions.

The results obtained on *patients* are summarized in Tables 2, 3, 4, 5, and 6. For statistical analysis the tests made after operation have been divided into groups. When oxygen consumption and respiration were studied, the most natural division of the data was into 3 groups of tests, these made 2 to 6, 7 to 11, and 12 to 21 days after operation. The data on cardiac output and pulse rate, however, were subdivided differently. Only few estimations of cardiac output were made because the early results looked so unpromising. The pulse rate data looked more promising, and we added several experiments in which pulse rate alone was measured. Accordingly data on the circulation were divided into 2 groups, those made 1 to 8 days and 9 to 19 days after operation. When more than one estimation was made on a single subject within one time period, these results were averaged so that *n*, as given in the tables, represents the number of patients, not the number of tests.

TABLE 2.—CHANGES IN RESTING VALUES DUE TO OPERATION

Date of results:	2nd to 6th day			7th to 11th day			12th to 21st day		
	mean	$\sigma$	n	mean	$\sigma$	n	mean	$\sigma$	n
Resp. rate per min. . . .	+2.8	4.8	10	+1.1	1.9	12	+1.3	2.6	11
Resp. volume, liters per min.	0	1.6	9	+0.1	0.6	11	+0.3	0.7	11
Resting metabolic rate, deviation % normal basal . .	-3	11	8	-2	17	10	-10	25	10

The statistics are derived from differences between results found after operation and those obtained before it. For example, in tests performed between the 2nd and 6th day after operation, the average respiration rate was 2.8 per minute greater than it had been before operation. None of the means is significantly different from zero.

The data obtained on our patients give information about the effect of convalescence from operative procedures on resting respiration and oxygen consumption which supplements our previous study on the resting circulation. These are recorded in Table 2.

TABLE 3.—ABSOLUTE VALUES FOR EXTRA OXYGEN CONSUMPTION AND EXTRA RESPIRATION DUE TO EXERCISE

	RESPIRATION DUE TO METABOLISM											
	Days after operation											
	Before operation			2 to 6			7 to 11			12 to 24		
	mean	$\sigma$	n	mean	$\sigma$	n	mean	$\sigma$	n	mean	$\sigma$	n
Extra oxygen, cc.	271	161	15	311	122	10	420	207	11	422	179	11
Extra respiration, l.	4.9	5.7	15	4.3	6.6	10	7.7	4.9	12	5.5	4.2	10

Statistics from data obtained during a mild exercise test.

TABLE 4.—CHANGES IN THE RESPONSE TO EXERCISE IN POSTOPERATIVE CONVALESCENCE

Date of results:	2nd to 6th day			7th to 11th day			12th to 21st day		
	mean	$\sigma$	n	mean	$\sigma$	n	mean	$\sigma$	n
Extra oxygen required for exercise in cc.	-25	188	10	+41	168	11	+41	207	11
Extra respiratory volume required for exercise in liters	-0.5	11	10	+2.1	9	12	+1.8	7	10

The statistics given are derived from differences between results found after operation and those obtained before it. For example, in tests made from the 7th to the 11th day after operation, the average oxygen needed to perform the work was 41 cc. greater than before operation. None of the means is significantly different from zero.

TABLE 5.—CHANGES IN THE RESPONSE OF THE CIRCULATION TO EXERCISE DURING CONVALESCENCE AFTER OPERATION

	1st to 8th day			9th to 19th day		
	mean	$\sigma$	n	mean	$\sigma$	n
Pulse rate per minute:						
Immediately after exercise	-3.0	7.9	11	-2.5	7.1	13
30 seconds after exercise	-0.6	6.2	10	+1.1	5.5	13
5 minutes after exercise	+5.1	8.0	11	+4.4	6.8	13
Cardiac output:						
Immediately after exercise, %	+2.0	4.0	5	-1.0	4.2	6
30 seconds after exercise, %	+5.0	2.8	5	+2.0	3.1	6
5 minutes after exercise, %	+3.0	5.4	5	-3.0	0.7	5

The statistics given are derived from differences between results found after operation and those obtained before it. For example, in data obtained between the 1st and 8th day after operation the pulse rate 5 minutes after exercise averaged 5.1 per minute faster than before operation. The mean in bold face type is significantly different from zero.

TABLE 6.—CHANGES IN THE "DYSPNEA RATIO" AND IN THE "DURATION OF INCREASED OXYGEN CONSUMPTION" AFTER EXERCISE IN POSTOPERATIVE CONVALESCENTS

	Days after operation								
	2 to 6			7 to 11			12 to 21		
	mean	$\sigma$	n	mean	$\sigma$	n	mean	$\sigma$	n
Dyspnea ratio	+0.4	0.08	9	+0.8	0.10	10	-0.3	0.12	9
Duration of incr. oxygen consumption, min.	+0.94	1.46	9	+0.95	1.04	10	+0.5	0.77	10

Means in bold face type are significantly different from zero.

To give readers a better idea of the results obtained with the exercise test the data have been recorded in two ways. In Table 3 statistics on the extra oxygen and respiration needed for the standard exercise are given, the averages being derived from data set up as are those in Table 1. This provides readers with a much needed impression of the nature of our results, but it is a poor method of arranging the data



for statistical analysis, and no one would be surprised to find that, as in this instance, the differences are not significant. In Tables 4, 5, and 6 the data are presented in such a way as to neutralize individual differences which may be present. In these compilations the values for each subject found before operation have been subtracted from the corresponding values found after it. The averages of these differences are given in Tables 4, 5, and 6, and one can thus ask himself the question whether the average change caused by the operation is significantly different from zero. This same method was used in the preceding paper, where an explicit example is given.

In analyzing the data on oxygen consumption and respiration we studied both the absolute values and the values per square meter of body surface. No improvement in the scatter resulted from the inclusion of the latter factor nor was significance attained, so the figures given in the tables are not divided by body surface.

**Discussion.** In a previous investigation we studied the effect of operative procedures on the circulation of resting subjects. Although not our primary object, the studies reported here permit us to add information about the effect of operation on the resting respiration and oxygen consumption. These data are summarized in Table 2, and statistical analysis shows that none of the changes found after operation is significant. It may be concluded, therefore, that the operative procedures had no effect on the respiration and oxygen consumption of subjects at rest.

The main purpose of this investigation was to answer the question whether the response to exercise was altered in postoperative convalescence. We speculated that a given amount of work might then be performed less efficiently, that is, with a larger consumption of oxygen in relation to the work performed, as has been demonstrated after more severe exercise when the performer is "out of condition."<sup>9</sup> From personal experience the senior author believed that when unwell, he tended to breathe more heavily for a given exercise than when in good health, so it was expected that respiration during a standard exercise would be greater during postoperative convalescence than before or after it. Our results, however, must be considered under two headings: (1) those concerned with the *amount* of the changes induced by the exercise and, (2) those having to do with the *duration* of these changes. The results of the first group were negative; that is, we were unable to demonstrate that convalescence had a significant effect on the amount of oxygen consumed, the mechanical efficiency, the volume of respiration, cardiac output, or pulse rate during mild exercise.

It is true that the average of these results is of some interest. Thus the average mechanical efficiency with which our patients performed the work was 10.9% before operation, 13% shortly after it, and then declined to 9.6% for the remainder of their stay in the hospital. Though the differences are not significant, one cannot but wonder whether the strain of the operation called out bodily reserves which at first increased the efficiency. Only after some days had elapsed was the reduced efficiency characteristic of convalescence revealed. The statistical

odds are almost 3 to 1 in favor of a decline in efficiency after the first postoperative week. If we had continued our work and studied a larger series of patients, significant differences might well have been attained. Our aim, however, was not to establish the decline in efficiency in convalescence, it was to devise a test for convalescence. For this purpose we have gone far enough to get our answer; no satisfactory test for convalescence can be developed by measurements of this kind. The variability inherent in the responses of individual subjects overwhelms the small changes which are caused by convalescence, and the latter frequently cannot be detected.

Our data on the duration of the changes induced by exercise contrast with our inability to demonstrate significant differences in the amount of these changes. During convalescence pulse rate, respiration, and oxygen consumption, although not unduly increased by the exercise, return to normal more slowly after it than was the case before operation. Thus the average dyspnea ratio,<sup>5</sup> a measure of the prolongation of increased respiration, is increased during convalescence. Reaching a maximum in the 7th to 11th day after operation the difference is significant at that time; later the abnormality diminishes as the patient improves. Similarly, after operation the increased oxygen consumption of exercise returns to normal more slowly as the subjects take longer to pay their debt. Again this abnormality reaches a maximum in the period between the 7th to 11th day after operation when significance is attained, to decline as the patient improves.

Also, after operation, while the average pulse rate taken within 30 seconds of cessation of exercise is not abnormal, that taken 5 minutes later is faster during convalescence than it was before operation. In the first week after operation the average difference just misses significance, the probability being 7.5 in 100, while in the following period significance was attained.

Obviously the objective abnormalities of convalescence are to be sought in the duration of the effects of exercise rather than in their amount. This is in accord with the observations of others in many conditions of ill-health.<sup>9</sup> The slow return of the pulse rate to normal after exercise has been the basis of many fitness tests. Increased dyspnea ratios have been reported in the unfit,<sup>5</sup> and a prolongation of the time required to pay the oxygen debt is a well known feature of heart disease.<sup>8</sup>

While we have been able to demonstrate significant abnormalities in convalescence by the use of averages, it is another matter to design a test which would detect these abnormalities in an individual seen for the first time in that state. The variability of the responses of our subjects was so great that we see no possibility of designing a satisfactory test for the detection of convalescence, and so of its duration, by a test of the type we have employed. Perhaps this should have been expected as abnormalities not detected by mild exercise could be demonstrated by more vigorous exercise in Hunt and Dufton's series. However, we question whether it would be proper to subject patients recently operated upon to exercise as severe as these authors employed.

Since the effects of postoperative convalescence are so overwhelmed by the variation inherent in our subjects, it was natural that we should give thought to the causes of this variation. One such cause, inherent in all weight-lifting exercise tests, consists of the differences in the way the work was done. In our test we can easily calculate the mechanical work performed, 600 foot-pounds per minute in each test. However, the conclusion that this value truly represented the effort exerted by the subjects would be erroneous. Other factors are of great importance. For instance, the calculation assumes that the bar is lowered without effort, which is certainly not the case as the subject opposes its free fall so that it will not strike his chest. To lift the bar with a jerk requires more effort also than if it is done with an easy motion, so the true effort exerted cannot be readily measured, and we have no assurance that our subjects were applying exactly the same effort in successive tests. That the manner of doing work affects the efficiency of a muscle's performance is well known.<sup>9,13</sup>

Attracted by the result obtained on R. M. on September 20, we calculated the correlation coefficient between the volume of respiration per minute before exercise and the extra oxygen needed for the standard exercise. Using all our data obtained on both normal subjects and patients, both before and after operation, we found significant negative correlation between these values. Apparently in our subjects deep breathing before exercise was followed by more efficient performance of mechanical work, and this raises some interesting physiologic questions far beyond the scope of this investigation.

We also sought for a relation between the oxygen consumption before exercise and the efficiency of its performance, but we found nothing significant.

**Summary and Conclusions.** By means of a standard mild exercise test we have sought for abnormalities during convalescence from surgical procedures.

Oxygen consumption, and volume, and rate of respiration have been determined before, during, and after standard exercise. Cardiac output (ballistocardiogram) and pulse rate were estimated before, just after, and 5 minutes after the same standard exercise.

Measurement of the *magnitude* of the changes induced by the exercise, revealed no significant differences which could be attributed to convalescence. However, when attention was given to the *duration* of the changes induced by the exercise, the averages showed significant differences, the increased oxygen consumption, respiration, and pulse rate declining to the resting level more slowly during convalescence than before operation.

The respiration and oxygen consumption of subjects at rest were not significantly changed during convalescence.

The variability in the physiologic response to exercise was so large that a test of the type used gives no promise of providing a satisfactory measure of the duration of convalescence in individual cases. However, the slow return to normal of pulse rate, respiration, and oxygen consumption after exercise is over may have some value as an indica-

tion of persisting abnormality in certain individuals and will provide significant differences when data obtained from a series of 10 or more cases are averaged.

## REFERENCES

1. CHRISTENSEN, E. H.: *Skand. Arch. f. Physiol.*, **76**, 88, 1937.
2. DICKINSON, S.: *J. Physiol.*, **67**, 242, 1929.
3. DILL, D. B., *et al.*: *J. Physiol.*, **71**, 47, 1931.
4. FISHER, R. A.: *Statistical Methods for Research Workers*, 7th ed., London, Oliver & Boyd, 1938.
5. HUNT, G. H., and DUFTON, D.: *Quart. J. Med.*, **13**, 165, 1919-20.
6. IRVING, L.: *Physiol. Rev.*, **19**, 112, 1939.
7. IRVING, L., SCHOLANDER, P. F., and GRINNELL, S. W.: *Proc. Physiol. Soc. of Philadelphia, Am. J. Med. Sci.*, **202**, 915, 1941.
8. MEAKINS, J. C., and LONG, C. N. H.: *J. Clin. Invest.*, **4**, 273, 1927.
9. SCHNEIDER, E. C.: *Physiology of Muscular Activity*, 2nd ed., Philadelphia and London, Saunders, 1941.
10. STARR, I., and SCHROEDER, H. A.: *J. Clin. Invest.*, **19**, 437, 1940.
11. STARR, I., and MAYOCK, R. L.: *Am. J. Med. Sci.*, **210**, 701, 1945.
12. TAYLOR, C.: *Am. J. Physiol.*, **135**, 27, 1941.
13. WIGGERS, C. J.: *Physiology in Health and Disease*, 4th ed., Philadelphia, Lea & Febiger, 1944.

## COARCTATION AND ACUTE DISSECTION OF THE AORTA ASSOCIATED WITH PREGNANCY

By THOMAS D. KINNEY, M.D.

INSTRUCTOR IN PATHOLOGY, HARVARD MEDICAL SCHOOL, AND ASSOCIATE PATHOLOGIST,  
PETER BENT BRIGHAM HOSPITAL

R. EMERSON SYLVESTER, M.D.

RESIDENT PHYSICIAN, NEWTON HOSPITAL

AND

SAMUEL A. LEVINE, M.D.

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, AND PHYSICIAN,  
PETER BENT BRIGHAM HOSPITAL  
BOSTON, MASSACHUSETTS.

(From the Medical Service of the Newton Hospital, the Departments of Pathology of  
the Peter Bent Brigham Hospital and Harvard Medical School)

THE present report is that of a case of coarctation of the aorta with a dissecting aneurysm in a 23 year old pregnant white woman. Instances of coarctation of the aorta associated with pregnancy are unusual: Mendelson,<sup>1</sup> in a review of the literature in 1940, was only able to find 26 cases and added 3 cases of his own; a more complete review has uncovered 9 additional cases<sup>2</sup> besides the one reported here, bringing the total number of reported cases of associated pregnancy and coarctation of the aorta to 39. However, dissection of the aorta occurred in only 2 of these cases, those reported by Strassman<sup>3</sup> and by Katz.<sup>4</sup> The present case, then, is the third in which dissection occurred in coarctation of the aorta in a pregnant woman and is the first in which the diagnosis was made before death.

**Case Report.** The patient, a 23 year old white, married, pregnant woman (K 1178) entered the Newton Hospital, Feb. 10, 1944, on the orthopedic service because of severe pain in her neck that extended down her left arm.

The patient stated that she was 6½ months pregnant. She had had frequent examinations during this period and was told that her blood pressure and

urine were normal. The pressure recordings were 140/90, 120/70 and 144/80 during the 3 months before admission. Six days before the present episode she visited a local obstetrician to make arrangements for further prenatal care and delivery. At this time, physical examination revealed a slight systolic murmur over the base of the heart which was interpreted as a functional murmur. It was thought the thyroid gland was somewhat enlarged. No pulsation was noted in the right neck. The blood pressure in the right arm was 160/100. No other abnormalities were noted at this time.

On the morning of admission she was stooping over a sink about to wash her hair when she was called and lifted her head suddenly with a sideways motion. This was immediately followed by sudden pain in the back of her neck extending from the occiput down the spine to a point midway between the scapulæ. Pain was also experienced down the left arm as far as the elbow and in the back of her throat. The pain was dull in nature but steadily increased in severity. It was not aggravated by motion. She was able to move her head in all directions except extreme flexion. Rest did not improve the condition. A buzzing sensation developed in her right neck. The patient became apprehensive and a physician was summoned who advised hospitalization.

The *family history* was not remarkable. The patient's mother, father and four brothers were living and well.

The *past history* showed that development was normal. She had always been active in sports and had noted no symptoms except for a pulsation in her right neck following exertion. As a child she had mumps, whooping cough, scarlet fever and chicken-pox. She had no other illnesses except a history of joint pains at the age of 16 that did not confine her to bed.

*Present History.* On admission the pulse was 64, temperature 98.4° and respirations 20. The blood pressure in the right arm was 100/90 and in the left arm 138/88. No readings could be obtained in attempting to take the blood pressure of the legs. The skin of the face seemed somewhat suffused. There was a slight fulness over the thyroid area. There was a marked pulsation in the right side of the neck at a point just above the junction of the sternocleidomastoid muscle and clavicle, and a palpable thrill and systolic impact over this area. Posteriorly, there was tenderness over the cervical vertebræ. There was moderate limitation of flexion of the neck but movements of the neck were not restricted otherwise. The breasts showed only the usual changes associated with pregnancy. Lungs showed no râles but there was slight dulness and decreased breath sounds at the right base. The heart was enlarged to percussion both to the right and left with increased dulness at the base of the heart, especially at the left upper border of the breast. The rhythm was regular and the sounds were forceful and of good quality. A Grade II systolic murmur was heard over the base, especially at the pulmonary area, and a fainter systolic murmur at the apex. There was an impact to the sounds at the base. A faint but definite systolic murmur was heard between the vertebræ and the spine of the left scapula. A pulsating artery was felt beneath the rib in the left midback. The radial pulse on the right was weak and was of normal intensity on the left. Pulsations were absent in the abdominal aorta, femoral arteries and dorsalis pedis vessels. There was no pitting edema. The abdomen was enlarged and the fundus of the uterus was palpable just above the umbilicus. The fetal heart sounds were of good quality, the rate being 140.

*Laboratory Data* (during hospital stay). Hemoglobin, 78% (Sahli); red blood cell count, 3,590,000; white blood cell count, 13,900; a normal distribution of the white cells and no abnormal red or white blood cells. The N.P.N. was 38.8 mg. and the blood cholesterol 259.2 mg. per 100 cc. The fasting blood sugar was 107 mg. per 100 cc. The blood Hinton was negative. Two electrocardiograms (Feb. 11 and 14, 1944) showed slight left ventricular preponderance; the second showed slight but definite elevation of ST<sub>1</sub> + ST<sub>2</sub> and slight depression of ST<sub>4</sub> (Fig. 1). Roentgen ray of the chest on the 1st hospital day showed the heart to be enlarged and the lungs to be clear; the 4th

and 5th hospital days, Roentgen rays showed a further increase in the size of the heart and width of the mediastinal shadow (Fig. 2).

*Hospital Course.* The patient was seen by one of us (S. A. L.) who made a diagnosis of congenital coarctation of the aorta with acute dissecting aneurysm. At this time she appeared fairly well. The patient was moved out of the general ward into a single room and arrangements were made to perform an

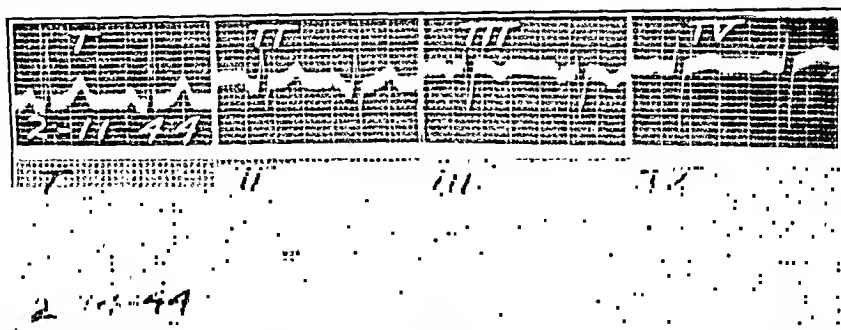


FIG. 1.—Upper electrocardiogram (4 leads) taken Feb. 11, 1944; lower record taken Feb. 14, 1944. Note slight elevation of ST<sub>1</sub> and ST<sub>2</sub> and slight depression of ST<sub>4</sub>.

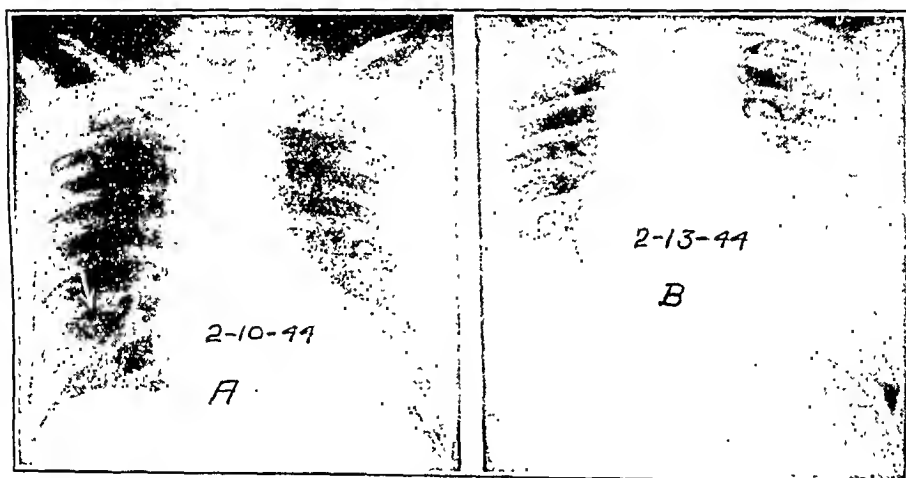


FIG. 2.—A, a 7 foot Roentgen ray plate, taken Feb. 10, 1944, shows moderate general cardiac enlargement and some prominence of ascending aorta. There is slight but definite notching of the ribs especially of the right eighth rib posteriorly. (See arrow.) B, Roentgen ray (bed plate taken Feb. 13, 1944) shows considerable further enlargement of the heart and aortic shadow.

emergency Cæsarean section, as it was feared that the aneurysm might suddenly rupture into the pericardial sac. She remained in the hospital for 5 days. During this time she complained of attacks of pain over the base of the skull. Other times, pain was present in the neck and over the precordium. The chest pain was accentuated by deep breathing. There were 2 minor exacerbations of pain in the base of the skull and precordium on the 2nd and 3rd days of her stay. These required morphine, which afforded relief. The evening of Feb. 12, 1944, she suddenly went into collapse, became unconscious, was pulseless and the blood pressure was unobtainable. Some minutes after this she became conscious, complained of severe pain at the base of the skull and in the anterior chest, for which she was given morphine ( $\frac{1}{8}$  gr., and atropine,  $\frac{1}{16}$  in.). Improvement followed, so that the blood pressure returned to the previous level.

During the late afternoon of the 5th hospital day (Feb. 14, 1944) there was a sudden loss of consciousness. The patient became cyanotic and suffered a mild convulsive seizure. Respirations were deep and slow and she died 3 minutes later. A postmortem Cæsarean section was performed and a viable baby obtained which weighed 2 pounds 15 ounces. The baby lived for 3 hours.

*Autopsy.* The body was that of a normally developed well-nourished young white female. The pertinent pathologic findings were in the heart and aorta.

The pericardial cavity was tense and distended by approximately 750 cc. of liquid and clotted blood. The serosal surfaces of the parietal and visceral pericardium were covered by deposits of fibrin. The heart weighed 390 gm. There was a bicuspid aortic valve which measured 7 cm. in diameter. The cusps were well formed and showed no evidence of thickening. The remainder of the heart was not remarkable. The aorta, at a point 9 cm. above the aortic valve and 0.8 cm. distal to the mouth of the left subclavian artery, narrowed



FIG. 3.—Aorta showing point of coarctation. (See arrow.)

abruptly to a diameter of 3 mm. (Fig. 3). This diameter was maintained for a distance of 5 mm. when the aorta abruptly widened to a circumference of 5.2 cm. There was a ragged tear in the aorta which began at a point 1 cm. above the aortic valve and extended up and laterally across the aorta for a distance of 3.5 cm. (Fig. 4). Blood had dissected through the tear and back into the pericardial cavity. Dissection had also extended up the ascending aorta, between layers of the media involving the innominate and right carotid arteries. The lumen of the carotid artery was partially occluded. The aorta distal to the point of narrowing was somewhat smaller but otherwise not remarkable.

*Microscopic Examination.* Multiple sections of the aorta were taken both proximal and distal to the point of coarctation as well as from the point of rupture. These were fixed in 10% formalin and stained with hematoxylin eosin and Weigert's elastic tissue stains. The intima in all sections was thin



FIG. 4.—Aorta showing point of rupture. (See arrow.)

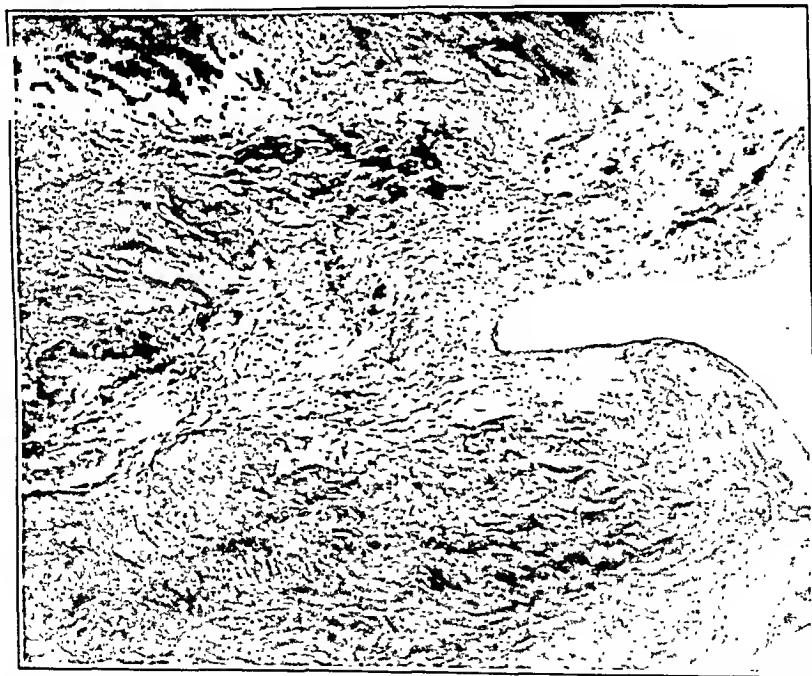


FIG. 5.—The ascending aorta at the point of rupture showing the marked loss of elastic tissue and replacement by scar tissue. (Hematoxylin and eosin,  $\times 97$ .)



and regular and showed no evidence of atheroma or other changes. The internal elastic lamella was intact and of uniform thickness.

The media in all sections of the aorta proximal to the point of coarctation showed marked changes. There were many areas in which there was loss of both muscle cells and elastic tissue. Elastic tissue stains showed breaks in the continuity of the elastica in these areas. In the sections taken from the ascending arch of the aorta and particularly in those near the point of rupture the loss of elastic tissue was especially severe (Fig. 5). In these areas there were numerous cavities filled by mucoid-like material from which the elastic tissue had completely disappeared (Fig. 6). These cavities were bordered by apparently normal media. In one area, near the point of rupture, approximately a third of the media was devoid of elastic tissue and the defect was replaced by loose fibrous scar tissue which was relatively avascular (Fig. 8).

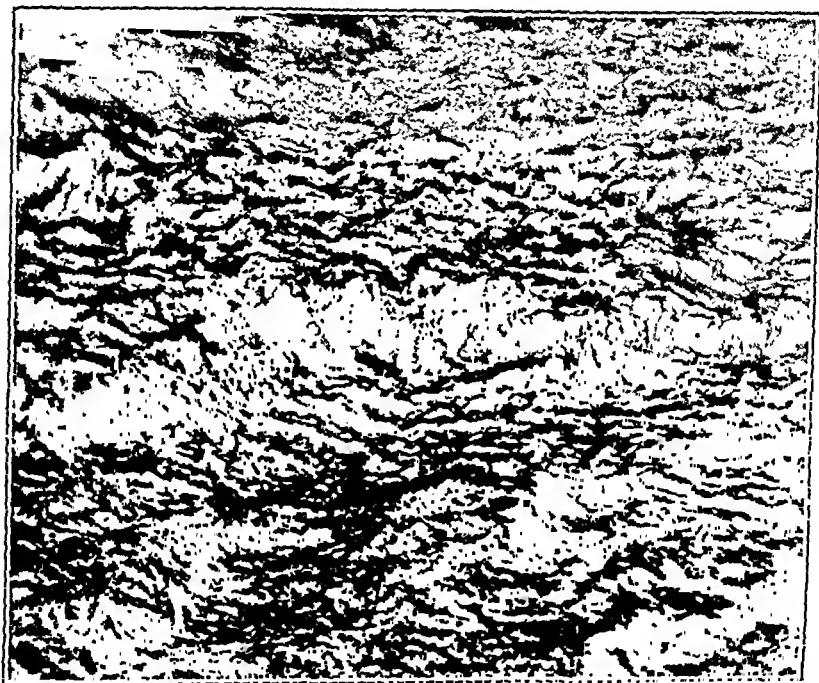


FIG. 6.—The ascending aorta demonstrating the marked cavity formation in the media. (Hematoxylin and eosin,  $\times 125$ .)

Similar smaller areas were present throughout the sections taken from the aortic arch. No adventitial lesions could be demonstrated. It should be noted that no evidence of inflammation was found in any of the sections of aorta studied. No lesions of the media were present in the sections taken from the aorta distal to the point of coarctation.

Sections of the myocardium were not remarkable except for the pericardial surface. Here, there was recent blood clot and the subpericardial space was moderately infiltrated by neutrophils and mononuclear cells.

Postmortem examination of the fetus showed marked pulmonary atelectasis. The heart, aorta and other organs were normal.

**Comment on Pathologic Findings.** The changes in the media of the aorta proximal to the point of coarctation were similar to those described by Erdheim,<sup>5</sup> Moritz<sup>6</sup> and others and to which the name "Medionecrosis aortae idiopathica cystica" has been given. This

lesion has not been noted often in coarctation of the aorta. Harrison<sup>7</sup> has reported a case in which this type of medial degeneration was present in the arch of an intact coarcted aorta. Gloggeniesser<sup>8</sup> described a case of coarctation in which dissection was associated with medial necrosis. Abbott and Hamilton,<sup>9</sup> in a review of the literature in 1928, found 33 cases in which there was spontaneous rupture of the ascending aorta and in 13 of these the microscopic examination of the wall of the ascending aorta adjacent to but not involved in the rupture was made. In 1 case, the wall of the aorta was considered to be normal while in all the other aortæ there were marked changes in the media, which were described as consisting of interruption and diminution of the elastica with hyaline and occasionally fatty degeneration. These changes were considered by Abbott and Hamilton to be evidence of inherent weakness of the media. It should be pointed out that all of the cases discussed by Abbott and Hamilton were reported before Erdheim's description of medial necrosis cystica and therefore it is possible that many of these cases would today be considered examples of medial necrosis rather than of developmental defects of the media. Of particular interest in the present case, and in Harrison's case was the fact that the medial lesion was present in the aorta proximal to the point of coarctation and absent in that portion of the aorta distal to the coarctation. In a third unreported case seen by one of us this combination of circumstances was also true.

In a review of dissecting aneurysm in young individuals, Schnitker and Bayer<sup>10</sup> found that there was a high incidence of congenital narrowing of the aorta varying in degree up to coarctation. The large number of young pregnant women in their review led them to speculate concerning the possible relationship between altered lipid metabolism and acute dissection of the aorta. This problem needs further investigation.

**Clinical Discussion.** Acute dissection of the aorta and coarctation of the aorta are individually not very rare. However, the presence of both occurring in a young pregnant woman is quite uncommon, and only 2 other such cases have been reported. It is of interest that the clinical antemortem diagnosis was not difficult. The onset of sudden severe pain in the throat and the back of the neck which also involved the upper back and left arm directed attention to the possibility of a vascular accident. In the case reported by Katz<sup>4</sup> similar pain in the throat and neck was a prominent feature. The routine examination, which revealed absent femoral and abdominal pulsations, quickly focussed attention on the possibility of coarctation of the aorta. This readily explained the basal systolic murmur and led us to listen to the interscapular region where the same murmur was audible. Furthermore, confirmatory evidence was obtained when a pulsating artery was detected in the left midback, and no blood pressure reading could be made out in the legs. It is of interest that this clinical diagnosis was made even though the Roentgen ray examination first overlooked the changes in the ribs. After the diagnosis of coarctation had been established, the obvious explanation for the symptoms appeared to be

a rupture of the aorta. The palpable thrill in the region of the right carotid artery and the decrease in blood pressure in the right arm indicated that the dissection had extended to partly occlude the right carotid and innominate arteries. As rupture into the pericardial sac is a frequent complication of dissecting aneurysm of the ascending aorta, the final outcome in this case was anticipated.

**Summary.** A case is reported in which an acute dissection of a coarcted aorta occurred in a young pregnant woman. Death took place abruptly as a result of rupture of the dissection into the pericardium. This is the first instance in which the complete anatomic diagnosis was made antemortem.

#### REFERENCES

1. MENDELSON, C. L.: Pregnancy and Coarctation of the Aorta, *Am. J. Obst. and Gynec.*, 39, 1014, 1940.
2. (a) HAMILTON, B. E., and THOMPSON, K. J.: *The Heart in Pregnancy and the Childbearing Age*, Boston, Little Brown, 1941. (b) BRAMWELL, C., and LONGSON, E.: *Heart Disease and Pregnancy*, London, Oxford Univ. Press, 1938. (c) WALKER, C. M.: Pregnancy and Labor in Case of Congenital Coarctation of the Aorta, *Brit. Med. J.*, 1, 190, 1943. (d) DUSTIN, C. C., and WEYLER, H. L. C.: Coarctation of the Aorta Associated With Pregnancy, *Rhode Island Med. J.*, 24, 59, 1941. (e) TURINO, T. R., and WALLACE, J. T.: *Résumé of Cardiac Disease in Pregnancy for a Five Year Period With a Report of a Case of Coarctation of the Aorta*, *Am. J. Obst. and Gynec.*, 45, 526, 1943. (f) STRAYHORN, W. D.: Coarctation of the Aorta: A Case Report With Observations on the Cardiac Output During and After Pregnancy, *Medical Papers, Henry Christian Birthday Volume*, Baltimore, Waverly Press, pp. 134-141, 1936.
3. STRASSMAN, G.: Der Plötzliche Tod bei Stenose des Isthmus Aortæ, *Beitr. z. gerichtl. Med.*, 5, 91, 1922.
4. KATZ, H.: Über den plötzlichen natürlichen Tod in Schwangerschaft, Geburt und Wochenbett, *Arch. f. Gynäk.*, 115, 293, 1922.
5. ERDHEIM, J.: (a) Medionecrosis aortæ idiopathica, *Virchows Arch. f. path. Anat.*, 273, 454, 1922. (b) *Ibid.*, 276, 187, 1930.
6. MORITZ, A. R.: Medionecrosis Aortæ Idiopathica Cystica, *Am. J. Path.*, 8, 717, 1932.
7. HARRISON, F. F.: Coarctation of the Aorta of the Adult Type Associated With Cystic Degeneration of the Media in the First Portion of Arch, *Arch. Path.*, 27, 742, 1939.
8. GLOGGENGIESER, W.: Sogenannte Spontanruptur der Aorta bei Isthmusstenose und Medianekrosen der Aorta, *Frankfurt Ztschr. f. Path.*, 56, 11, 1941.
9. HAMILTON, W. F., and ABBOTT, M. E.: Coarctation of the Aorta of the Adult Type, *Am. Heart J.*, 3, 381, 574, 1928.
10. SCHNITKER, M. A., and BAYER, C. H.: Dissecting Aneurysm of the Aorta in Young Individuals, Particularly in Association With Pregnancy With Report of a Case, *Ann. Int. Med.*, 20, 486, 1944.

## COMBINED ACUTE VASCULAR LESIONS OF BRAIN AND HEART.

### A CLINICAL-PATHOLOGIC STUDY OF 15 CASES

BY GEORGE A. RACE, M.D.

AND

JAMES R. LISA, M.D.

NEW YORK 17, NEW YORK.

(From the First Medical Division and the Laboratory of Pathology, City Hospital Welfare Island, Department of Hospitals, New York)

THERE has been little mention in medical literature concerning the simultaneous occurrence of acute cardiac infarction and acute cerebrovascular accident. In 1937, Dozzi<sup>2</sup> reviewed 107 autopsies of hemor-

rhage, thrombosis or embolism of the brain. He found that 12 cases (11.2%) had an associated coronary thrombosis. He also stated that among 41 cases of coronary thrombosis, 12 (29%) had an associated cerebral vascular lesion. He gave no details of the pathology, nor did he describe the acuteness or chronicity of the lesions. In 1939, Dozzi<sup>3</sup> reported electrocardiograms taken on 66 cases of hemiplegia. In this group, there was evidence of coronary thrombosis in 8 (12.1%). He commented on the close approximation of the figures in the material from autopsy and of the cases of hemiplegia. Among the 66 cases, 15 came to autopsy, including 4 of the 8 cases diagnosed as coronary thrombosis. The coronary thrombosis was verified in these 4 instances, in 2 of which coronary occlusion was of recent origin and in 2, of remote origin. Meakins and Eakin,<sup>4</sup> in 62 cases of coronary occlusion, found an associated cerebral thrombosis in 6.4%. Among 83 autopsies of coronary thrombosis, Parkinson and Bedford<sup>5</sup> reported 1 case of cerebral embolism. Conner and Holt,<sup>1</sup> in a study of 287 cases of myocardial infarction, found 14 cases (4.9%) with associated cerebral emboli.

The present report is a review of 100 consecutive autopsies performed at City Hospital from 1938 to 1944 in which either an acute myocardial infarction, with or without coronary thrombosis, or an acute cerebral vascular accident was found. In the entire series, there were 15 cases with combined acute vascular lesions of both brain and heart.

Of the 100 cases, 90 were in whites and 10 in negroes. The sexes were equally divided, 50 in each group. The ages ranged from 25 to 88 years, the youngest patient being a white female 25 years old; the oldest, a white female 88 years old. The age distribution in decades was as follows: 20-29, 2; 30-39, 3; 40-49, 13; 50-59, 24; 60-69, 29; 70-79, 20; 80-89, 9. Of the 15 cases with the combined lesions, 9 were in women and 6 in men. It is unusual to find a female predominance in any statistics associated with acute coronary occlusion and particularly so in reference to its complications. Indeed, White<sup>7</sup> states that the male sex is more often affected, "at least to a serious degree," by coronary disease than is the female. Their average age was 65.4 years, the youngest being a male 34 years old, and the oldest, a male and a female, both 82. All the patients were white.

Among the 15 cases with the combined lesions of heart and brain, the cerebral lesions proved to be of various characters. The most frequent lesion found in the brain was cortical petechial hemorrhages, usually of widespread, unilateral distribution. See Figure 1. Massive intracerebral hemorrhage was almost as frequent. There were only 2 cases of extensive encephalomalacia. Of the cardiac lesions, there were 6 cases of acute coronary thrombosis with infarction and 9 instances of extensive acute myocardial infarction without thrombosis. The details of these findings are given in Table 1.

The clinical features in the cases with the combined lesions of brain and heart are of particular interest. The presenting symptomatology was more frequently neurologic in nature. The cardiac symptomatology was less frequent. There were some cases in which symptoms

referable to both organs were present, but usually the neurologic signs were more striking. There were only 2 cases completely lacking in neurologic signs and symptoms. There were 8 cases with complete absence of cardiac complaints. The chief presenting symptoms and signs are given in Table 2.

TABLE 1.—PATHOLOGIC FINDINGS OF HEART AND BRAIN

Brain	Acute coronary thrombosis	Acute myocardial infarction without thrombosis
Small intracerebral hemorrhages . . . . .	1	1*
Massive intracerebral hemorrhages . . . . .	0	4
Massive encephalomalacia . . . . .	2	0
Cortical petechial hemorrhages . . . . .	2	3
Intracerebral petechial hemorrhages . . . . .	0	1*
Cortical and intracerebral petechial hemorrhages . . . . .	1	1

\* Both cerebral lesions found in the same patient.

TABLE 2.—PRESENTING SIGNS AND SYMPTOMS

Coma . . . . .	8
Hemiparesis . . . . .	1
Hemiplegia . . . . .	8
Aphonia . . . . .	2
Chest pain . . . . .	5
Cardiac decompensation . . . . .	2
Absent neurologic findings . . . . .	2
Absent cardiac findings . . . . .	8

The correct clinical diagnoses of combined lesions of brain and heart were made in only 2 instances. In 2 other cases, they were suspected. In 2 cases, the cardiac infarction was correctly diagnosed and in 7 instances, the correct diagnosis of the cerebral lesion was made. Neither lesion was suspected in 2 cases. That the cerebral lesion was more often correctly diagnosed may be attributed to the fact that the neurologic signs and symptoms were predominant.

The brief histories and pathologic findings of 4 illustrative cases are presented.

**Case Abstracts.** CASE 1. A 52 year old white male had had previous twinges of precordial pain. On the night of admission, he awoke from sleep, vomited and felt a choking sensation over the upper part of his chest. His breathing became labored and he lost consciousness. Physical examination revealed a comatose, non-cyanotic individual. His heart sounds were good. Blood-pressure: 170/110. His reflexes were normal and equal except for bilateral Babinski signs. An electrocardiogram showed an acute anterior coronary occlusion. Blood sugar: 236 mg. per 100 cc.; blood N.P.N.: 35 mg. per 100 cc. The temperature and pulse rose, the patient went rapidly downhill and he died 24 hours after admission.

AUTOPSY revealed an acute coronary thrombosis of the anterior descending branch of the left coronary artery with myocardial infarction. There was an aneurysmal dilatation of the left ventricle and a rupture of the left ventricle at the junction of the lateral ventricular wall with the aneurysm. There were also cortical and intracerebral petechial hemorrhages of the left frontal and temporal and right frontal and parietal lobes, and of the pons, medulla and the deep portions of the island of Reil (see Fig. 1).

CASE 2. A 71 year old white male had had frequent attacks of cardiac decompensation. Three years ago, there was an attack of loss of speech from which he recovered in 5 months. On admission, he was speechless and stupor-

ous. His face was twisted to the right. The liver was palpable and tender. The heart showed a normal sinus rhythm with no murmurs. Blood pressure: 230/175. The deep reflexes were absent in the right arm and the Babinski sign was positive on the right. Blood sugar: 87 mg. per 100 cc.; blood N.P.N.: 32 mg. per 100 cc. An electrocardiogram revealed disease of the left ventricular muscle. The patient became dysarthric and then anarthric. The pulse and temperature rose, signs of consolidation developed at the right base and the patient died 9 days after admission.

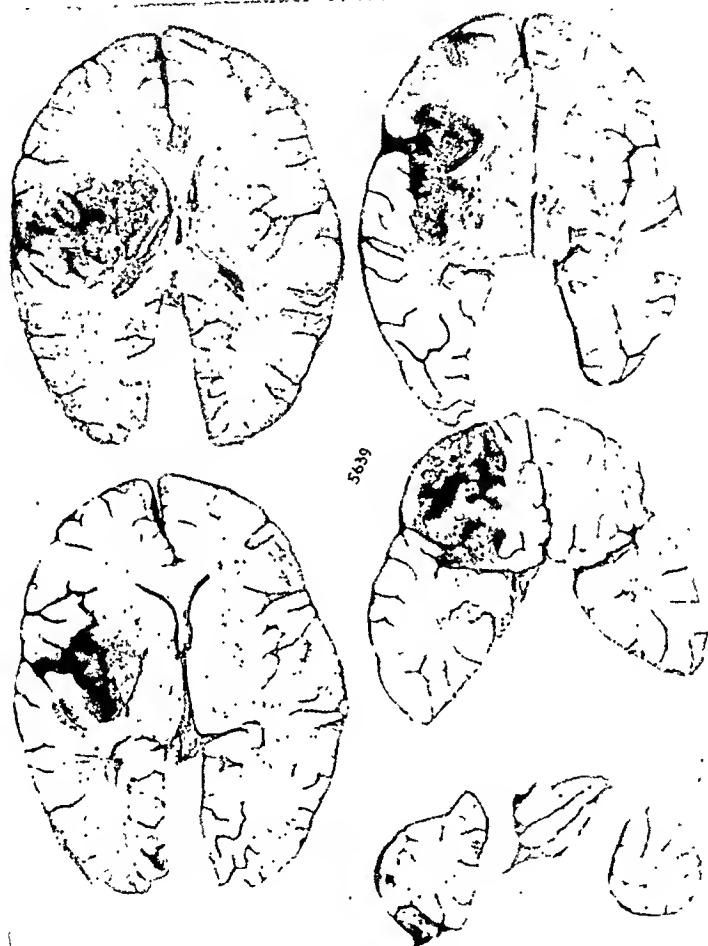


FIG. 1.—Photographs of a brain illustrating extensive petechial cortical hemorrhages involving the frontal lobe, the island of Reil, the occipital lobe and the basal nuclei.

AUTOPSY revealed acute cardiac infarction of the left ventricle without thrombosis. The brain showed cortical atrophy of the right cerebrum and superior gyrus of the left temporal lobe, cerebral arteriosclerosis and acute massive intracerebral hemorrhage of the left basal nuclei, involving the internal capsule.

CASE 3. An 82 year old white female was found lying on the floor, unable to speak or to move her right arm or leg. She had had a similar stroke 14 years ago. On physical examination, the heart was found to have a normal sinus rhythm. There were no murmurs. Blood pressure: 220/100. There were occasional dry râles at the right base. There was a right hemiplegia with a

right facial paralysis. The Babinski sign was positive on the right. The temperature and pulse rose, moist râles developed in the chest, the patient became cyanotic and she expired 3 days after admission.

AUTOPSY revealed an acute cardiac infarction of the left ventricle and the distal portion of the interventricular septum without thrombosis. There was a hemorrhagic area in the left basal ganglion region including the thalamus, the posterior portion of the lenticular nucleus and the posterior limbs of the internal capsule and the external capsule. There was also atrophy of the right parietal-occipital region.

CASE 4. An 82 year old white male fell from a chair, and developed a motor aphasia and paralysis of the right upper and lower extremities. Shortly afterwards, he lost consciousness. He was comatose on admission. Physical examination showed a right facial paralysis. There were bilateral basal râles. The heart was enlarged to the right. No murmurs were heard. Blood pressure: 150/100. There was paralysis of the right arm and leg and the Babinski sign was positive on the right. The patient developed dyspnea and cyanosis with loud coarse râles and a rise in temperature to 103°. He expired 4 days after admission.

AUTOPSY revealed acute cardiac infarction of the apex of the left ventricle without coronary thrombosis and multiple areas of infarction in the wall of the right ventricle. In the brain were found cortical and intracerebral hemorrhages of the frontal and parietal lobes and of the lenticular nucleus.

During the course of this investigation, it was found that in another 5 of the 100 reviewed cases, the clinical manifestations led to the diagnosis of a cerebral accident with a resultant hemiplegia. In each of these cases, an acute myocardial infarction was found and in each case the brain, both on gross examination and on section, failed to reveal any acute vascular lesion. All of these patients were males, their average age was 65.2 years. Four of the patients were comatose, all 5 exhibited hemiplegia and none of them presented symptoms or signs referable in any way to an acute cardiac lesion.

The brief histories and pathologic findings of 2 illustrative cases are presented.

CASE 5. A 68 year old white male, while seated in a chair, suddenly slumped to the floor and developed paralysis of the left leg, arm and face. There was no loss of consciousness but his speech was thick. The patient had had a stroke 5 years before. Physical examination revealed a semistuporous patient with a left hemiplegia and a positive Babinski sign on the left. The heart sounds were of poor quality. There was a regular sinus rhythm. No murmurs were heard. Blood pressure: 135/88. During the patient's 15 days in the hospital, the neurologic findings remained unchanged. For the last 48 hours, he was stuporous, then comatose and had a terminal fever of 103°.

AUTOPSY revealed an acute thrombosis of the anterior descending branch of the left coronary artery with progressive myocardial infarction. On gross examination and on section, the brain revealed 2 well-demarcated areas of softening and atrophy, 1 in the inferior portion of the island of Reil and the other in the posterior portion of the right occipital lobe. Otherwise, the brain was negative.

CASE 6. A 74 year old white male fell twice and developed difficulty in speaking on the day before admission. Physical examination revealed a patient with a left seventh nerve paralysis. The rhythm of the heart was irregular. There were no murmurs. Blood pressure: 150/110. The reflexes were normal and equal. The Babinski sign was negative. On his third hospital day, he was found in coma with signs of a left hemiplegia. The next day he developed diffuse râles through both lung fields. He expired 7 days after admission.

AUTOPSY showed a progressive myocardial infarction without thrombosis. On gross examination, the brain was negative.

**Comment.** The evidence from these cases indicates that clinical findings alone are not sufficient basis for establishing the co-existence of the two acute lesions. The etiology of the hemiplegia in these cases is an interesting point for speculation. Perhaps the best explanation is the development of a temporary anoxemia of the brain caused by the sudden drop in blood pressure which usually accompanies an acute cardiac infarction. The fact that 4 of the 5 patients were comatose may be cited in support of this theory.

**Discussion.** It is obvious from the data presented that acute myocardial infarction may be masked by the presence of an associated acute cerebral vascular accident or by neurologic signs having no demonstrable pathologic explanation. It is equally obvious, therefore, that every case with neurologic evidences of a cerebral lesion should also be considered as a case of acute coronary occlusion until proven otherwise. If such an error can occur in one out of every 5 cases, then this caution is certainly warranted. The discovery of an associated acute myocardial infarction will change the treatment and may well alter the prognosis.

In reviewing the cause of death in these 20 cases, it was found that in 11, a major factor in the demise of the patient was an acute broncho- or lobar pneumonia. The pattern for this ultimate termination was seen in the case histories of Patients 2, 3, 4 and 6. The high incidence of this terminal factor raises the pertinent question as to whether the prophylactic use of sulfa drugs should be employed in all cases of cerebral accidents and acute cardiac infarctions.

**Summary.** 1. A review is presented of 100 consecutive autopsies with either an acute myocardial infarction or an acute cerebral vascular accident in which both the brain and the heart were examined.

2. Fifteen cases (15%) were found to have both acute myocardial infarctions and acute cerebral vascular accidents.

3. Five cases were found to have neurologic signs pointing to a cerebral accident. The brains in all 5 cases were negative on gross examination and on section, whereas acute myocardial infarctions were demonstrated in all of them.

4. It is suggested that in every case with neurologic evidences of an acute cerebral vascular lesion acute cardiac infarction be carefully considered and explored.

5. The suggestion of the use of sulfa drug prophylactically in these cases is raised, in view of the high incidence of terminal lobar and broncho-pneumonia.

#### REFERENCES

1. CONNER, L., and HOLT, E.: *Am. Heart J.*, 5, 705, 1930.
2. DOZZI, D.: *AM. J. MED. SCI.*, 194, 824, 1937.
3. DOZZI, D.: *Ann. Int. Med.*, 12, 1991, 1939.
4. MEAKINS, J., and EAKIN, W.: *Canad. Med. Assn. J.*, 26, 18, 1932.
5. PARKINSON, J., and BEDFORD, D.: *Lancet*, 1, 34, 1928.
6. SHERF, D., and BOYD, L.: *Cardiovascular Disease*, St. Louis, Mosby, p. 210, 1939.
7. WHITE, P. D.: *Heart Disease*, New York, Macmillan, p. 414, 1935.



# THE RELATIONSHIP BETWEEN CELLS AND PLASMA IN CULTURES OF THE BUFFY COAT FROM HUMAN BLOOD

BY GEORGE DRAPER

CYNTHIA PIERCE

AND

C. W. DUPERTUIS

NEW YORK, NEW YORK.

(From the College of Physicians and Surgeons, Columbia University and Presbyterian Hospital)

SINCE the recent report by Draper, Ramsey and Dupertuis<sup>2</sup> on variations in behavior of cultured leukocytes from individuals of different constitution types, further observations have been made of the cellular and humoral relationships in such preparations. Previous workers in the field of tissue culture have been faced with the question of whether the cellular component of the explant or the plasma medium is responsible for modifications in the form and migration of out-wandered cells. Walton,<sup>5</sup> working with rabbit testicle, thyroid and kidney tissue in various rabbit plasmas, concluded that the plasma alone was responsible for variations in cell growth. It should be noted, however, that Walton's experiments were concerned with fixed tissues of different organs. Carrel<sup>1</sup> believes that monocytes act as delicate indicators of the quality of the serum media in which they may be growing. He points out that changes in the plasma which the monocyte reaction detects may be related to the serum provider's age, state of nutrition, or pathologic condition.

The foregoing remarks bear upon two problems. The first concerns the relative importance of cells and plasma as factors in determining the character of cell morphology and behavior. The second raises the question of the extent to which a given individual's cells exhibit individual specificity. Species specificity of the cells is known to exist and Landsteiner's blood groups point to subspecies specificity in red cells as well. As yet, however, there is little evidence bearing on species specificity in the white cells of the blood. The possibility that some such cellular identity exists, however, receives support from Landsteiner's<sup>3</sup> observation based on precipitin reactions: ". . . in spite of cultivation of chicken tissues in foreign plasma over an extended period there was no loss of species specificity." But, to the question of individual specificity, the work of Loeb<sup>4</sup> on living tissue transplants brings convincing evidence. In line with Loeb's demonstrations, recent findings in this laboratory, based upon observations of human leukocytes incubated in autogenous and homogenous plasmas, point not only to a factor supplied by the plasma component of the culture but also to the positive contribution by the leukocytes as well.

**Experimental Procedure.** The technique used here for preparing tissue cultures has been described previously.<sup>2</sup> The necessity for washing the cells

in order to free them completely from their own adherent film of autogenous plasma before transplant into foreign plasma is evident.

Two experiments were planned to investigate the part played by plasma and cells in determining the extent and rate of migration as well as individual cell form and conduct. A total of 127 individuals supplied the blood; some of the recovered clinical cases were in good health.

As an early use of this method of investigating specificities in white blood cells, this study did not attempt to identify, in the hematologic sense, the various types of leukocytes in the buffy coat culture. In a previous paper<sup>2</sup> we reported that polymorphonuclears and large mononuclear cells differed greatly in behavior and survival time. These differences were important factors in what we have presumed to be constitutional cell patterns. The small lymphocytes, of all the white cells, have consistently displayed almost no visible change of aspect or special activity.

In an attempt to exclude extraneous factors from influencing the size of the areola we have standardized, as far as possible, the size of the explant, the amount and proportions of the medium, and have drawn the blood at a generally constant time after breakfast in the morning. We also ran a few experiments to determine how much explant size influenced areola size. It turned out that this influence was slight. Apparently during the first 3 hours the cells migrate mainly from the surface layers of the explant.

In the first experiment, blood specimens from 127 individuals (8 normal, the rest representing 19 different diseases) were studied in pairs (88 instances), threes (23), and fours (16). Four cultures were prepared for each pair. One culture for each member of the pair was composed of its own plasma and cells (autogenous) and one of its own cells incubated in its partner's plasma (homogenous). In the groups of threes and fours the same procedure was carried out so that the buffy coat of each blood sample was cultured in its own and in each of its companion plasmas.

TABLE 1.—EFFECTS OF AUTOGENOUS AND HOMOGENOUS PLASMAS UPON  
3 DIFFERENT BUFFY COATS

Cells	Plasma	Clinical diagnosis and constitutional type	Blood type	Areola		Activity of cells	Cellular morphology
				Width	Density		
S	s	Tuberculosis linear, muscular type	A	Nar.	Med.	Extr.	Cells with small thin projections; at 24 hours many broad, long, pale cells (see Fig. 1, 1)
S	r	....	..	Nar.	Med.	Mod.	Many small, round cells, and many large bizarre, pale cells; at 24 hours long, thin cells (see Fig. 1, 2)
S	t	....	..	Nar.	Med.	Mod.	Cells with 1 or 2 blunt pseudopodia; at 24 hours many very long, pale cells (see Fig. 1, 3)
R	r	Myocardial infarction	A	Wide	Thick	Mod.	Majority of cells with numerous small blunt pseudopodia appearing very knobby (see Fig. 1, 4)
R	s	....	..	Wide	Med.	Mod.	Much cell death and many pale, broad cells; occasional long cells becoming very numerous at 24 hours (see Fig. 1, 5)
R	t	....	..	Wide	Med.	Slight	Much cell death and many round cells; at 24 hours clumps of round cells (see Fig. 1, 6)
T	t	Poliomyelitis lat., stocky type	B	Very nar.	Thin	Mod.	Cells with 1 or 2 blunt pseudopodia; at 24 hours many broad, pale cells, only occasional long thin cell
T	r	....	There were insufficient T cells to complete this cross				
T	s	....	..	Very nar.	Thin	Slight	Much cell death; many round cells; at 24 hours many round and many irregular pale cells

Buffy coat is designated by capital letter. Plasma designated by small letter. Explant, R, S, T.

For the second experiment, 42 buffy coats from blood of 42 of the patients were cultured (a) in the plasma of an individual who had suffered from infan-

tile paralysis 16 years previously, and (b) in its own plasma. In both experiments all the cultures were incubated at 37° C. and were observed at 3 and 24 hour intervals. Areola width and density, individual cell morphology, and the activity of the migrating cells were recorded. (See Tables 1 to 4.) In addition, the red cells of each blood sample were classified according to the Landsteiner method.

TABLE 2.—EFFECT OF AN INTERCHANGE OF LEUKOCYTES AND PLASMA UPON AREOLA SIZE

Cells	Plasma	Clinical diagnosis and constitutional type	Blood type	Areola		Activity of cells	Cellular morphology
				Width	Density		
W	w	Chr. myelo. leukemia	O	Nar.	Med.	Mod.	Very large cells, clumped together and regular in shape
W	x	....	..	Nar.	Med.	Mod.	Very large cells, clumped together and regular in shape
X	x	Infec. mononucleosis	O	Nar.	Med.	Mod.	Many small round cells; many cells with 1 or 2 blunt pseudopodia
X	w	....	..	Very wide	Very thick	Mod.	Many small round cells; many cells with 1 or 2 blunt pseudopodia

Buffy coat designated by capital letters. Plasma designated by small letters. Explant, W, X. Plasma, w, x.

TABLE 3.—AN INSTANCE OF CROSSED LEUKOCYTES AND PLASMAS SHOWING NO CHANGES

Cells	Plasma	Clinical diagnosis and constitutional type	Blood type	Areola		Activity of cells	Cellular morphology
				Width	Density		
Y	y	Diabetes mellitus	B	Med.	Med.	Mod.	Many cells; many long cells; at 24 hours no long cells
Y	z	....	..	Med.	Med.	Mod.	Many cells; many long cells; at 24 hours no long cells
Z	z	Hypertension, contact dermatitis	O	Very wide	Med.	Mod.	Many pale, broad, angular cells; some cells with very sharp projections
Z	y	....	..	Very wide	Med.	Mod.	Many pale, broad, angular cells; some cells with very sharp projections

Buffy coat designated by capital letters. Plasma designated by small letters. Explant, Y, Z. Plasma, y, z.

TABLE 4.—THE EFFECT OF ONE PLASMA (t) UPON THE LEUKOCYTES OF 3 DIFFERENT INDIVIDUALS

Cells	Plasma	Clinical diagnosis and constitutional type	Blood type	Areola		Activity of cells	Cellular morphology
				Width	Density		
L	l	Mixed type ulcer-G.B.	O	Med.	Thick	Mod.	Round, regular cells; no change at 24 hours
l.	t	....	..	Wide	Thick	Extr.	Bizarre cells and much debris; at 24 hours many long, pale cells
C	c	Inf. mononucleosis	O	Nar.	Thin	Slight	Many round cells, with little knobs; at 24 hours many long, pale cells
C	t	....	..	Nar.	Thin	Mod.	A few ghost cells; at 24 hours many round cells but no long, pale cells
J	j	Coronary occlusion	O	Wide	Thin	Extr.	Knobby cells; at 24 hours several long, pale cells and also clumps of round cells
J	t	....					No change

Buffy coat is designated by capital letter. Plasma designated by small letter. Explant, L, C, J. Plasma, l, c, j, t.

Observations. FIRST SERIES. The varying patterns produced in leukocyte cultures by an interchange of plasmas are illustrated in photomicrographs 1 to 9 of the migrating cells at the periphery of the areola.

Figure 1, 1, shows the tissue culture pattern produced by the leukocytes, cultured in their own plasma, from an individual with pulmonary tuberculosis. Figure 1, 2 and 3, illustrates the effects of two different plasmas upon these same leukocytes. An occasional elongated cell may be seen in Figure 1, 2, whereas, in 3, the vast majority of cells are elongated and bizarre in shape. Figure 1, 4, depicts the culture pattern of a patient with coronary disease. The typical knobby cells found in such cultures may be seen in the right hand corners. Figure 1, 5 and 6, illustrates the effects of two different plasmas upon this case. Very little change can be noted in 5, but in 6 marked clumping of small round cells appears. The buffy coat of an individual with peptic ulcer is shown in Figure 2, 7. Figure 2, 8 and 9, shows the modification of this pattern by homogenous plasmas. It would seem, from the foregoing observations, that the plasma medium was the dominant factor in these reactions. In contradistinction, however, Figure 1, 3 and 6, and Figure 2, 9, dispute this conclusion. All 3 cell samples, originating from different human subjects, were planted in the same alien plasma medium. Comparison of the bizarre, elongated cells of Figure 1, 3 (and to a lesser extent, of Figure 2, 9) with the clumped, sharply outlined, small, round cells of Figure 1, 6, indicates that the leukocytes also express themselves vigorously as determining factors in the reactions.

Types and variations in cell plasma crosses are revealed in Tables 1 to 4. In certain instances cellular morphology appeared to be greatly influenced by plasma change (see Table 1). This table presents 3 individuals whose buffy coats were each grown in autogenous and homogenous plasmas, but the effect on cell morphology by alien plasma is notable.

On the other hand, Table 2 demonstrates the influence of foreign plasma upon areola size with no changes in cell morphology. Each of the 2 buffy coats, when cultured in their respective plasmas, developed narrow areolas. However, when the leukocytes from an individual with infectious mononucleosis were incubated in the leukemic plasma a very wide and very thick areola was produced. It is further demonstrated by this table that reciprocal action in a given pair does not necessarily occur. Thus, when one buffy coat of a pair is crossed with the other's plasma, there may often be no effect whatsoever. In such a case the culture pattern remains as it originally formed in its own plasma. It does not follow, however, that the buffy coat of the second partner will, when crossed with the first partner's plasma, take on the characteristics of the other's pattern. In still another instance of cell plasma cross (Table 3) no modification in areola size or cellular morphology was observed.

It appears from this first experiment that almost any areola size, and any pattern of cell form and conduct may result from crossing cells and plasmas, and that there is adequate evidence that the cells contribute to the pattern quite as much as the plasma.

SECOND SERIES. The effects of one person's plasma upon the buffy coats of 42 different individuals were studied in the second part of the investigation.



FIG. 1.—1, White blood cells and plasma from S, an individual with pulmonary tuberculosis. 2, White blood cells, S, in plasma, r, from an individual with myocardial infarction. 3, White blood cells, S, in plasma, t, from an individual who had had poliomyelitis. This plasma was used in several instances (see 6, 9, 11). 4, White blood cells and plasma from R, an individual with myocardial infarction. Typical knobby cells are seen, one at upper right and the other at the lower left. 4A, Another case of coronary occlusion showing the knobby cells to good advantage. 5, White blood cells from R, in plasma, s, from an individual with pulmonary tuberculosis. 6, White blood cells, R, in plasma, t, from an individual who had had poliomyelitis. (Magnification, in general,  $\times 480$ .)

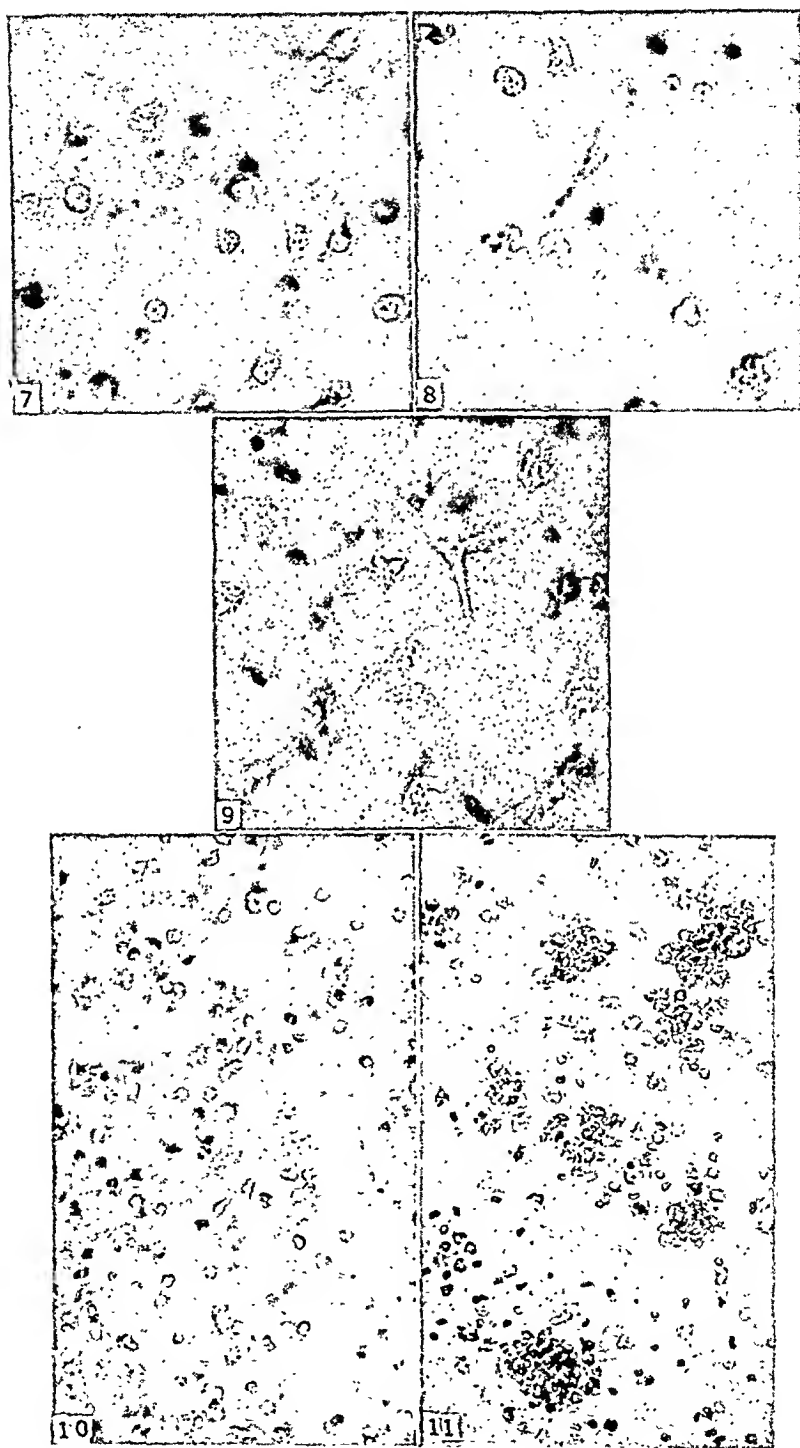


FIG. 2.—7, White blood cells and plasma from Oo, an individual with peptic ulcer. 8, White blood cells, O, in plasma, r, from an individual with myocardial infarction. This plasma was also used in 2 and 8. 9, White blood cells, O, in plasma, t. 10, White blood cells and plasma from an individual with rheumatic fever. 11, White blood cells, same as 10, in plasma, t. Note the clumping mentioned on page 744. (Magnification, in general,  $\times 480$ .)

Explants from each case were prepared and incubated under standardized conditions in their own and in the test plasma from an individual who had been the subject of infantile paralysis. Great variations occurred throughout this series. Of the 42 buffy coat cultures studied, 13 were not affected, 19 were slightly modified, and 10 were greatly changed. In some instances areola size was markedly influenced, in others cell morphology was altered, and in some samples clumping occurred which resembled red cell agglutination. In this connection it might be noted that Carrel<sup>1</sup> described similar clumping appearance in chicken monocytes in pathologic plasma. This phenomenon may be seen in Figure 2, 11. Figure 2, 10, shows the same buffy coat in autogenous plasma. At present there is no evidence to explain these white cell clumping reactions or to determine whether the alien plasma or cells contribute most emphatically to the phenomenon. As Figure 2, 11, demonstrates, it bears a close resemblance to erythrocyte agglutination. In both experiments, however, no correlation between the isoagglutinins of the plasmas and the buffy coat cultures was found.

**Discussion.** The foregoing paragraphs have described 2 experiments to investigate the rôle played by the cells and plasma in buffy coat cultures of leukocytes: the first, to explore crosses between cells and plasma of different human subjects; the second, to demonstrate the effects of one person's plasma upon the cells of many individuals. Crosses of cells and plasmas between 2 or more persons may result in variations from each one's basic cell plasma culture pattern, and the degree of these changes may extend from nothing (Fig. 1, 4 and 5) to one of extreme diversity (Fig. 1, 1 and 3). From the observations here reported we believe that the plasma is not the sole determinant of any given cell culture pattern. A significant part in the complex biologic reactions which produce the various cultures must also be attributed to the leukocytes. At present the relative importance of the two factors is not known. But, if the cells do contribute positively to the combined reaction, with plasma from whatever source, they can only do so because of some inherent factor or factors which they bring to the combination. In our original paper<sup>2</sup> reporting on tissue cultures of the buffy coat of bloods taken from patients whose constitutional types contributed to their development of certain illnesses, it was stated: ". . . in each areola the individual cells may display characters of size, form and behavior quite as specific as those which stamp the individual as a whole." On this basis further observations have made it possible to recognize with increasing frequency and to allocate to its proper source the buffy coat culture presented for diagnosis. Variations in correctness may be explained partly by Loeb's demonstration that not all tissues of an individual exhibit the same specificity, and partly by the fact that cell response in tissue culture is usually less violent than in direct tissue to tissue transplants. However, since the leukocytes are especially active in immunity reactions, it might be expected that they would exhibit a high degree of tissue specificity and sensitiveness to changes in their accustomed media.

If, then, independent specificity exists in each cell, the latter's capacity either to be modified or to be resistant to an alien plasma expresses that individual identity. To anyone who views these cells in the living state, there can be no doubt that the leukocytes from each individual behave in a distinctive way.

**Summary.** 1. In a first series, the leukocyte buffy coat from each of 127 patients was grown in both autogenous and homogenous plasma samples. The crosses were made at random in pairs, threes, and fours.

2. In this series (No. 1) variations occurred which ran from no apparent change to extensive modifications of areola size and cell behavior.

3. A second series of buffy coats were treated similarly except that the homogenous plasma for 42 cultures came from 1 individual. This person sustained an attack of infantile paralysis 16 years previously.

4. In this second series the variations caused by the single homogenous plasma were as striking as those observed in the first series. As this single plasma did not produce similar effects on all the 42 buffy coats, it was concluded that the plasma medium could not be held solely responsible for the ultimate configuration of the explants.

#### REFERENCES

1. CARREL, A.: Monocytes as an Indicator of Certain States of Blood Serum, *Science*, 80, 565, 1934.
2. DRAPER, G., RAMSEY, H. J., and DUPERTUIS, C. W.: Variations in the Behavior of Buffy Coat Cultures Among Individuals of Different Constitution Types, *J. Clin. Invest.*, 23, 864, 1944.
3. LANDSTEINER, K., and PARKER, R. C.: Serologic Tests for Homologous Serum Proteins in Cultures Maintained on a Foreign Medium, *J. Exp. Med.*, 71, 231, 1940.
4. LOEB, L.: *Biological Basis of Individuality*, Springfield, Thomas, 1945.
5. WALTON, A. J.: Variations in the Growth of Adult Mammalian Tissue in Autogenous and Homogenous Plasma, *Proc. Roy. Soc., London*, 87, 452, 1914.

---

## CHORIOCARCINOMA OF THE TESTICLE

By A. J. GILL, M.D.

G. T. CALDWELL, M.D.

AND

J. L. GOFORTH, M.D.

DALLAS, TEXAS

(From the Department of Pathology, Southwestern Medical College, and the Pathology Laboratory of St. Paul's Hospital)

DURING the past 18 months we have encountered 3 new cases of choriocarcinoma of the testicle. In our experience, these tumors in the male have been considerably more frequent than the corresponding tumor in the female. During the course of study of this group of relatively rare tumors, we have made several deductions that seem to us to merit brief discussion.

It is generally agreed by most observers that choriocarcinomas of the testicle are histologically identical with the analogous tumors in the female. It is furthermore agreed that they are almost always



associated with teratomas of the testicle. This feature of appearance of choriocarcinomas with well differentiated teratomatous tissue is well illustrated in two of our cases.



FIG. 1.—Case G4103, Area of choriocarcinoma of testicle with predominance of Langhans cells.



FIG. 2.—Case 56065. Section of the testicular tumor with Langhans and syncytial elements about evenly divided.

**Case Abstracts.** CASE 1. (No. 50702.) White male, age 55. Known duration of testicular swelling was 3 weeks, during which time there was slight tenderness and rapid increase in size of the mass. No history of trauma or anomalous development was obtained. The mass measured 6 x 5 x 4 cm. Ten days after orchidectomy a test for urinary gonadotropins was strongly positive. The patient expired 3 months following operation with clinical evidence of extensive pulmonary metastases.

Several poorly circumscribed hemorrhagic areas 2 to 3 cm. in diameter were seen on section through the region of the epididymis. Microscopically, the entire tumor, except for masses of typical choriocarcinoma, was obscured by hemorrhage and necrosis.

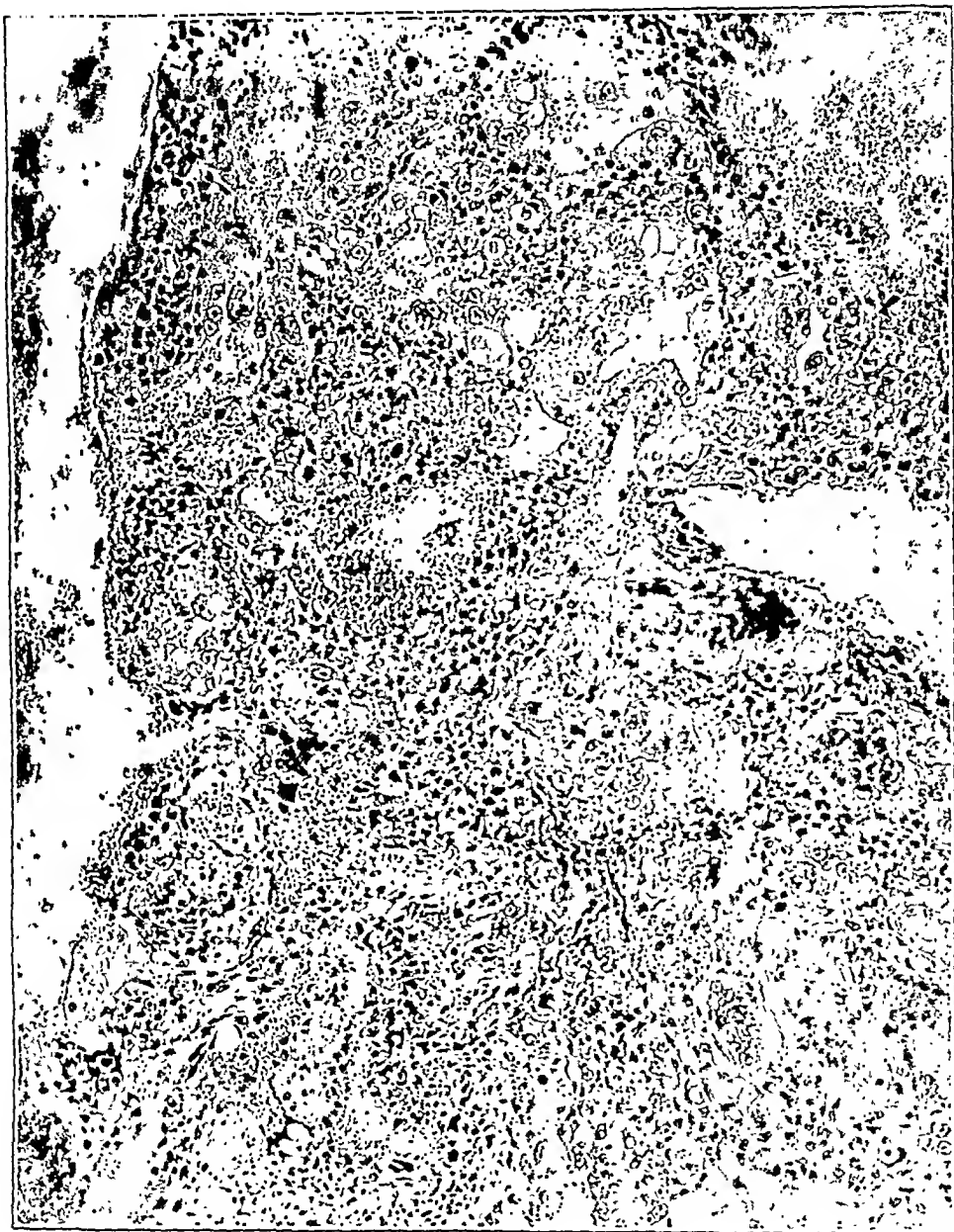


FIG. 3.—Caso 50702. In this area of choriocarcinoma of the testicle large syncytial masses are very conspicuous and numerous blood spaces are well illustrated.

CASE 2. (No. G4103.) White male, age 21. The patient noticed a small firm nodule in his left testicle. Two weeks later, the testicle, epididymis and enveloping membranes together with a section of the vas were removed. About 10 days postoperatively, a test for urinary gonadotropins was negative. No history of genital anomaly was obtained. At this writing, about 18 months after operation, he is said to be in excellent health.

A few small irregular hemorrhagic and cystic areas were noted in the region of the epididymis on gross section. Microscopically, epithelium-lined cystic spaces and well-formed gland structures are numerous. Much of the choriocarcinomatous portion is hemorrhagic and necrotic.

CASE 3. (No. 56065.) White male, age 30. This patient experienced a gradual enlargement of his right testicle for 8 to 10 months. On examination there was a testicular mass measuring  $6 \times 3 \times 3.5$  cm., and a hydrocele. No history of trauma or congenital anomaly was recorded. A test for urinary gonadotropins was not done and a follow-up report after 12 months is not available.

The gross specimen revealed the usual hemorrhagic and spongy appearance and firmer islets of what appeared to be cartilage. Sections showed a complex mixture of epithelium of various types and arrangements and several islands of cartilage in addition to the trophoblastic elements.

Added to the undeniable histologic similarity of these tumors to the choriocarcinoma of the female there is a functional similarity, in that substances responsible for the positive Aschheim-Zondek test are present in large amounts in the urine of males with this lesion. Hinman and Powell,<sup>3</sup> Freed and Coppock<sup>7</sup> and others have observed that the hormones from placental tissues may be similar functionally to some of those found in the urine in cases of testicular tumor.

Histogenesis of this tumor has occasioned much speculation in the past. Steinert<sup>13</sup> suggests that the teratomas arise from fetal blastomeres or from a fertilized polar body capable of reproducing all fetal layers. Our conception of the blastomere is that any cell of the subdivision of the fertilized ovum up through the morula stage of development and before the blastula stage may be so designated.

Ross<sup>11</sup> observed, in abdominal metastases, what she described as origin of syncytium and Langhans cells from small cubical darkly staining cells which also gave rise to carcinomatous tissue, and were found in blood-vessels, lymphatics, and peripheral sinuses of lymph nodes. She concludes that "formation of chorioepithelioma testis is the expression of a process of specific partial differentiation of these pluripotential cells." According to this author the choriocarcinomatous tissue arises by the metamorphosis of undifferentiated cells which also give rise to teratomatous structures. She felt that in the case reported by her it was not necessary to presuppose even the presence of fetal ectoderm.

Frank<sup>6</sup> suggests that metaplasia of any primitive ectodermal tissue might be responsible for choriocarcinoma. He believed, however, that reported presence of other teratomatous elements in metastases was serious argument against this. Cooke<sup>4</sup> stated that in the cases reported up until the time of his article, 3 had shown structures other than choriocarcinoma in metastases, although these other structures did not show malignant characteristics. This is difficult to explain by any hypothesis. Cooke suggests that a derivative from a germinal blastomere normally present in the testicle may form a teratomatous tumor containing elements of fetal membranes.

If one accepts the histologic and functional similarity of choriocarcinoma of the testicle and its analogue in the female, and since it appears probable that choriocarcinoma of the testicle is always asso-

ciated with teratoma, one might then assume that histogenesis in the male and in the female is the same. It seems probable that the only explanation lies in the assumption that these tumors of the testicle arise from a pluripotential cell with potential capacity similar to ovum and that the origin of choriocarcinoma from fetal ectoderm is not different from the origin of the same tumor in the female. That the germ, be it called blastomere, or simple multipotential cell, from which these tumors develop has potentialities similar to the fertilized ovum, seems evident because of the occurrence of easily recognized elements of two or more germ layers rather regularly in the primary tumors. It is probable that the multipotential cell from which these tumors are derived, is one that is normally present in the testicle. Since there are cells normal to the testicle which appear to fulfill all the criteria required, we believe that the idea of "inclusion" of blastomeres can be deprecated and support offered for another more generally accepted hypothesis, similar to that noted by Ewing,<sup>5</sup> Adams<sup>1</sup> and others, who have indicated spermatogenic cells as the probable origin of teratomatous tumors of testicle. In our opinion, it is entirely reasonable to accept the spermatogonium, the ancestor of the mature sperm in adult testicle, as the multipotential cell capable of giving rise to this group of tumors. It does not seem that there could be any insurmountable objection to the view that the spermatogonium has within itself the capacity to produce many structures since its descendants contribute much to the complete individual in the process of fertilization of another multipotential cell, the ovum.

Several unanswered questions arise, however, before the opinion is fully acceptable. One of these is the question: why does one never see a benign proliferation of trophoblastic tissues in the testicle? One also wonders why chorionic villi or benign hydatidiform mole is not observed in testicular tumors. In regard to this last question Kerwin<sup>9</sup> noted (without reference) that certain unsubstantiated cases of hyatid mole may have occurred.

The question of why choriocarcinoma of the ovary is rarely seen in association with teratoma of the ovary is also a troublesome one. Bettinger<sup>3</sup> has collected 4 cases, Seigmund<sup>12</sup> reported 1, and a few others have been noted. One case, described by Risel,<sup>10</sup> was at first considered a primary choriocarcinoma of the ovary but was finally thought to be secondary to a tiny healed lesion in the fundus of the uterus. That hormone influence may have some effect in choriocarcinoma testis is indicated by age incidence. As Cooke<sup>4</sup> has mentioned in his review of 47 cases, no choriocarcinoma was observed before puberty or after sexual activity had ceased. Steinert also notes the occurrence during sexual maturity. This suggests the possibility that some hormone stimulus may operate or that the cells of origin concerned may tend to proliferate normally with puberty and perhaps atrophy in senile individuals.

Because of the extremely high levels of hormone production and the expectation that the trophoblastic tissues elaborate hormones, it is easy to accept this activity of choriocarcinoma as a real and direct

function of the tumor. One is soon faced, however, with the necessity of explaining the increased levels of similar hormones produced by individuals with testicular tumors of types other than choriocarcinomas. One of the best established of the explanations for this phenomenon had been the assumption that most, if not all, of the testicular tumors were ultimately derived by differentiation from teratomas and that certain elements had so overgrown and displaced the teratomatous portion that tissues of the original teratoma were difficult to find by sectioning. The implication is that even well differentiated teratomas may elaborate hormones. We do not know of any evidence that teratomas in other parts of the body elaborate hormones, except in a rare case where specific endocrine tissues such as adrenal may be present. We wish to support a possible alternative hypothesis that the presence of a lesion of the testicle, even an adult teratoma, may depress testicular function and stimulate excretion of gonadotropic (pituitary) hormones in low titers, which are entirely different from chorionic gonadotropins. In short, it may well be that with the exception of the choriocarcinoma, none of the other testicular tumors, except possibly the very rare Leydig cell tumor, specifically elaborate any hormone whatsoever, and that appearance of various hormones in urine is the result of systemically deranged endocrine balance and/or the presence in the tumor of small amounts of hormone producing tissue which may not be discovered in routine study. A not dissimilar suggestion was expressed by Ross, who noted that a positive Aschheim-Zondek test was possible in tumors other than choriocarcinoma and made the further observation that male breast activity (presumably another evidence of hormone action) may occur with atrophy of testicle, melanoma of skin, and other tumors. As Twombly<sup>14</sup> pointed out, in his experience the chorionic gonadotropin occurs only when active tumor is present, although the castrate type of gonadotropin may exist long after a clinical cure of the tumor. He also notes that he considers the appearance of chorionic gonadotropin in seminomas as a further proof of the teratoid nature of this tumor and suggests that this hormone may be produced by tissue which he calls embryonal adenocarcinoma. Adams<sup>1</sup> actually demonstrated small amounts of what he believed might be trophoblastic tissue in several testicular tumors other than choriocarcinoma. He felt that presence of trophoblastic tissues in varying amounts might account for excretion of gonadotropic hormone in tumors which may appear to be different, but which probably have a common origin.

The chorionic gonadotropin which appears to be the type hormone elaborated by the tumor itself in choriocarcinoma probably should induce atrophy of the testicle because of the high concentration present, and atrophy is sometimes mentioned in patients with choriocarcinomas as well as others of the testicular tumors. Added evidence of endocrine dysfunction such as gynecomastia is often seen in victims of choriocarcinoma. Twombly has raised the question of whether or not there may be some shift in hormone balance which precedes rather than follows and may contribute to the development of testicular

tumors. Deranged testicular function, even prior to the beginning of malignant testicular tumors could stimulate the production of pituitary gonadotropin. This suggestion might explain occurrence of pituitary gonadotropic hormones in some tumors where trophoblastic tissues are not thought to occur.

**Conclusions.** After histologic study of 3 recent cases of choriocarcinoma of the testicle and consideration of part of the extensive literature on the subject, we think that there can be little doubt that these tumors arise from primitive cells which have essentially the same capacity as the developing ovum and that the malignant trophoblastic elements of these tumors are derived from ectoderm in the same way as the comparable tissue in ordinary pregnancy. It seems to us that the cells from which these tumors arise are multipotential sex cells normally present in the adult testicle. These cells are probably spermatogonia.

The differentiated elements of the teratoma in testicular tumors are probably not responsible for any hormone production which may be observed, and it is unlikely that any of the testicular tumors with the exception of the choriocarcinoma elaborate any hormone of themselves. In our opinion the finding of gonadotropic hormones in these other tumors suggests either undisclosed trophoblastic tissue or a systemic endocrine dysfunction which, as Twombly mentions, may have preceded the occurrence of the tumor.

#### REFERENCES

1. ADAMS, J. E.: *J. Urol.*, 47, 491, 1942.
2. AREY, L. B.: *Developmental Anatomy*, 4th ed., Philadelphia, Saunders, 1942.
3. BETTINGER, H.: *Zentralbl. f. Gynäk.*, 56, 1451, 1932; *Abstr., Am. J. Cancer*, 18, 770, 1933.
4. COOKE, J. V.: *Bull. Johns Hopkins Hosp.*, 26, 215, 1915.
5. EWING, J.: *Neoplastic Diseases*, 4th ed., Philadelphia, Saunders, 1940.
6. FRANK, R. T.: *J. Am. Med. Assn.*, 46, 249, 1906.
7. FREED, S. C., and COPPOCK, A.: *Proc. Soc. Exp. Biol. and Med.*, 32, 1589, 1935.
8. HINMAN, F., and POWELL, T. O.: *J. Urol.*, 34, 55, 1935.
9. KERWIN, T. J.: *J. Urol.*, 38, 91, 1937.
10. RISEL, W.: *Verhandl. d. deutsch. path. Gesellsch.*, 17, 386, 1914.
11. ROSS, J. M.: *J. Path. and Bact.*, 35, 563, 1932.
12. SEIGMUND, H.: *Arch. f. Gynäk.*, 149, 498, 1932; *Abstr., Am. J. Cancer*, 18, 494, 1933.
13. STEINERT, H.: *Virchow Arch. f. path. Anat. u. Phys.*, 174, 232, 1903.
14. TWOMBLY, G. H.: *Surgery*, 16, 181, 1944.

### HYDROMETROCOLPOS IN INFANCY—A CAUSE OF URINARY RETENTION, INTESTINAL OBSTRUCTION AND EDEMA OF THE LOWER EXTREMITIES

BY PAUL MORRIS, M.D.

PHILADELPHIA, PENNSYLVANIA.

(From the Pediatric Service, Mount Sinai Hospital)

ABDOMINAL tumors in female infants are not everyday occurrences in the practice of a physician, but when one meets with a huge cystic mass which can be cured by a simple surgical procedure after definite

diagnostic measures have been employed, and without laparotomy, one should be prepared for such a situation. If the condition is undiagnosed or misunderstood, laparotomy, with its attendant dangers in a young infant, may be unnecessarily employed.

Hydrometrocolpos in infancy was described in 1904 by Commandeur<sup>1</sup> who reported 1 case of his own and reviewed the literature in which 9 other cases were reported. The American literature, however, remained silent and such recent pediatric works as Brennemann's "Practice of Pediatrics,"<sup>2</sup> Schauffler's "Pediatric Gynecology,"<sup>3</sup> and Griffith and Mitchell's "Textbook of Pediatrics,"<sup>4</sup> fail to mention the occurrence of such a complication of a closed vagina before the onset of menstruation. It is briefly discussed in "Therapeutics of Infancy and Childhood"<sup>5</sup> as producing tremendous cystic tumors and is included in the bibliography of the article on Malformations of the Female Genital Organs in Holt's "Diseases of Infancy and Childhood."<sup>6</sup>

In 1940, Mahoney and Chamberlin<sup>7</sup> of Boston thoroughly described the combination of factors leading to such abdominal masses. They reviewed the literature and reported 3 cases of their own and 1 described to them by Dr. Camille Kereszturi of New York. One of their patients had other congenital deformities incompatible with life, another was misdiagnosed and resulted in a panhysterectomy, and a third was diagnosed correctly with the aid of injection of 20 cc. of diodrast followed by Roentgen ray studies. A cystogram showed a bladder compressed from above and behind and pushed forward. This child, 2 days after birth, presented a large, tense, round, lower abdominal tumor, reaching to above the umbilicus. A bulge at the vagina was thought to be a rectocele but later was shown to be the protruding cyst wall which bulged further when the baby cried. The hymen was not found, but a probe could be passed around the bulge to a depth of only 1 cm. The patient was cured by incision of the membrane with drainage of several ounces of turbid fluid. The examining finger could easily be inserted full length into the vagina but the markedly dilated wall contracted and gained tone almost immediately. The post-operative course was uneventful.

Kereszturi's patient was a 2 month old girl with diarrhea of 6 weeks' duration and a bout of urinary retention a week before admission to the hospital, July 8, 1937. On admission, after a day of fever, the temperature was 104° (R) and there was a cystic mass extending from the pubis to the umbilicus. A smooth mass protruded between the labia. There was urinary tract infection, and an intravenous urogram showed marked dilatation of the ureters and hydronephrosis. After 1 week, an exploratory laparotomy revealed a cystic mass behind the bladder, pushing the bladder and uterus upward. Pressure on the uterus caused the labial membrane to bulge. This membrane was incised and 2 ounces of milky fluid were released. The pelvic mass disappeared, the urinary tract became normal, and the patient was discharged well on August 26th, 7 weeks after admission. Kereszturi reported this case separately<sup>8</sup> and it appeared in print before the report of Mahoney and Chamberlin.

Because of these reports, Rosenblatt and Woolley were enabled to treat a case successfully, and they described the details in a brief case report in *Annals of Surgery* in 1943.<sup>9</sup> Their patient had a markedly dilated bladder which could be emptied by catheterization. The entire situation was cured by mere incision of the bulging vaginal membrane after Roentgen ray demonstration of the nature of the mass, following withdrawal of some of the fluid and injection of diodrast into the "cyst."

In addition to these reports of cases in infancy; there are 2 recent reports in the literature of similar cases in young girls just before the onset of the first menstruation. In Bowen's case,<sup>10</sup> a 12 year old "identical" twin whose twin sister had an open hymen was found to have an imperforate hymen and a symmetrical mass extending from the pelvis to the umbilicus. Rectally, a smooth walled cyst was felt in the midline. There was a pink spherical protrusion between the labia. The urine was normal, WBC 10,000, polys 80%. An incision into the hymen brought, instead of the expected blood, about 2 quarts of milky chyle-like fluid. The first menstruation appeared 5 months later, almost 3 months after the normal twin had first menstruated. This case brings up the question of whether or not some of the cases of hematocolpos with imperforate hymen might not be similar cases of hydrocolpos later made bloody by the first few menstrual bleedings. Tompkins reviewed 113 cases of imperforate hymen with hematocolpos in the literature and added 5 of his own<sup>11</sup> though Kereszturi found only a few to mention in her report. These cases are undoubtedly much commoner than those with non-bloody fluid, and one wonders why the latter are not oftener encountered. The other case of hydrometrocolpos in a premenstrual girl appeared in the German literature in 1941.<sup>12</sup> A 14 year old girl complained of abdominal pain and backache of 6 weeks' duration. The abdomen had become larger in the preceding 3 weeks. The hymen was imperforate. It was punctured and 50 cc. of cloudy "serous" fluid were withdrawn. A laparotomy was then performed and 2200 cc. of the same type of fluid were obtained by puncture of a large cyst-like structure which arose from the pelvis. Both fluids proved sterile when cultured and no acid-fast organisms grew out on the special culture. The fluid contained a moderate number of leukocytes but no epithelial cells. In spite of hormone therapy, the patient continued amenorrhic after operation although she was well otherwise.

Hydrometrocolpos has also been reported in a woman of 72 years with vaginal stenosis.<sup>13</sup> The presenting symptoms were inability to void and intestinal obstruction. The cause was undetermined after careful study of sections of the removed uterus and vagina, but "senile vaginitis" was offered as a possible etiology of the vaginal obstructions.

This tendency of the greatly distended vagina to displace the bladder upwards and to cause urinary obstruction is well illustrated by our own case.

**Case Abstract.** F. G., a 7 week old girl, developed swelling of the feet and a purplish discoloration of the lower extremities. This appeared rather sud-



denly during the course of a day in which only 2 slightly wet diapers followed after the baby awoke in the morning with a dry diaper. During the preceding 3 weeks, the mother had noted considerable straining as if the infant were trying to expel a stool at each feeding and that the stools had become ribbon-like in form. The day before, a few blood flecks had appeared in the stool. Many changes of formula had been ordered by the attending physician in order to relieve the difficulty. Two physicians saw the patient during the day of her scanty urinary output. The first ascribed her trouble to constipation and the second suspected intussusception because of the presence of a mass in the lower abdomen and the blood flecks in the stool.

When the infant was first seen by the author, there was obvious pitting edema of both lower extremities, which were purplish in color. This edema and discoloration extended upwards over the lower abdomen about half way to the umbilicus. There was a large cystic mass extending upwards from the pubis and apparently slightly more towards the right side and reaching to 2 cm. above the umbilicus. In addition, there was a peculiar bulge at the vulva, cystic in appearance, pointing anteriorly, somewhat resembling a rectocele with distended viscus pushing into it. There was no visible urethral meatus but catheterization was attempted in order to rule out a distended bladder as the cause of the abdominal "tumor". A small metal catheter was inserted blindly anterior to the vulvar bulge and it entered the urethra easily. A small spurt of clear urine appeared but no more could be obtained even with pressure on the abdominal mass. Rectal palpation revealed a bulging cystic mass anterior to the rectum. In view of the seemingly empty bladder, the abdominal mass was thought to be a cyst or a bladder diverticulum. The swelling and discoloration of the skin of the lower abdomen and lower extremities were interpreted as being due to pressure by the mass on the pelvic veins. It was felt that needle puncture of the vulvar bulge was somewhat risky because there seemed to be a hollow viscus behind it.

Hospitalization and laparotomy seemed to be the most conservative measures. The surgical consultant agreed that an abdominal exploration was indicated and he promptly performed a laparotomy under open ether anesthesia. In spite of the failure of catheterization to obtain more than a few cc. of urine, the large mass proved to be urinary bladder, tremendously distended. A catheter was again inserted into the urethra and no urine flowed until very great direct pressure was exerted on the distended bladder. When the bladder was partly emptied, a second mass appeared behind it. This was recognized as distended uterus and vagina and then only was the true nature of the difficulty recognized. Pressure on this mass, which was only about 5 cm. in diameter, caused an increased tension in the vulvar bulge which was then incised externally. A considerable amount (not measured) of a thin, slightly milky fluid escaped, and the mass collapsed, allowing easy emptying of the rest of the urine from the bladder. The fluid contained some white blood cells but the culture was sterile. Urine obtained the day after operation contained no leukocytes and only an occasional RBC. The baby survived the operation and was doing well until the operative wound disrupted a week later. The eviscerated intestine was replaced with difficulty. A fecal fistula later developed and death followed an operation to relieve an apparent obstruction 34 days after the first operation.

Supportive therapy included many intravenous injections of plasma and blood. Sulfadiazine was followed by a morbilliform eruption, but sulfasuxidine was well tolerated when it was used after the development of the fecal fistula.

**Comment.** While this case can be listed as an operative mortality, it can safely be said that "error in judgment" played a part. The laparotomy could have been avoided if the failure of the bladder to empty when catheterized had not thrown everyone off the proper diagnostic track. This very fact prompted publication of this paper in an effort to acquaint a wider group of physicians with a condition

which has been generally neglected by the text books on pediatrics and gynecology. Mahoney and Chamberlin<sup>7</sup> go into some detail in attempting to explain the development of the type of fluid present in these cases. It is their feeling, backed by some embryologic data,<sup>16</sup> that there is present an imperforate vagina similar to an imperforate rectum or anus, entirely apart from and above the hymen. One of their cases and that reported by Cranwell,<sup>14</sup> were autopsied and showed the atresia to be above the normal location of the hymen. Bonnet's case<sup>15</sup> also had a normal hymen with a vaginal occlusive membrane above. Cranwell<sup>14</sup> quotes Pazzi as saying that the true pathology in most cases where a thin membrane closes the vagina is not imperforate hymen but failure of perforation of the vagina.

During the first 2 weeks of life, there is marked activity of the cervical glands and the vaginal epithelium resembles the adult type, due to circulating estrogen derived from the mother.<sup>17</sup> Along with these changes, one occasionally finds slight vaginal bleeding in the newborn and, rather regularly, enlargement of the breasts. However, the cervical glands become less active and the vaginal epithelium becomes less keratinized after 2 weeks of age. Thus, there would have to be abnormal activity of the cervical or uterine glands to produce so large an amount of fluid as is found in the older children with hydrometrocolpos. Possibly, the two factors must be present together to produce the condition we are discussing—both obstruction of the vaginal orifice and an unusually large amount of circulating estrogenic hormones. It would be interesting to note if these patients presented unusual breast enlargement after birth.

The Italian literature<sup>18</sup> contains references to the experimental production of hydrometra in animals. The fluid in some of the cases in infants has been reported to contain "glucose."<sup>1</sup> Although Dobszay<sup>17</sup> reported finding no glycogen in the vaginal epithelium of children and older infants, it is regularly present in that of adults.

**Summary and Conclusions.** The literature relating to hydrometrocolpos is reviewed and a new case is reported. This case presents a new feature, *viz.*, edema and cyanosis of the lower extremities due to pressure on the pelvic vessels.

There is evidence that imperforate hymen is not the cause of the vaginal closure in these cases, but that failure of perforation of the vagina due to arrested embryologic development, such as one finds in imperforate anus, occurs. The peculiar direction of the vaginal bulge in this case supports such a probability.

The condition is recognized in the newborn if the vagina and uterus are sufficiently distended to cause pressure on the bladder and urinary retention. Otherwise, the condition might not be recognized until just before the menarche when there would again be increased activity of the cervical and uterine glands.

The large accumulations of bloody material in some cases of hematometrocolpos after only one or two periods of abdominal cramps might represent cases of preëxisting hydrometrocolpos into which the first menstrual blood has flowed.

Patients with hydrometrocolpos should not be subjected to laparotomy, as simple incision of the vaginal membrane entirely relieves the condition. Preliminary aspiration by needle of some of the cyst fluid and injection into the cyst of 20 cc. of diodrast followed by AP and lateral Roentgen ray views (as suggested by Mahoney and Chamberlin) will clearly establish the diagnosis in doubtful cases.

## REFERENCES

1. COMMANDEUR, M.: Bull. Soc. d'obstet. de Paris, 7, 54, 1904.
2. BRENNEMANN: Practice of Pediatrics, Hagerstown, Md., W. F. Prior, 1944.
3. SCHAUFFLER, G. C.: Pediatric Gynecology, Chicago, Year Book Pub., 1942.
4. GRIFFITH, J. P. C., and MITCHELL, A. G.: The Diseases of Infants and Children, 3rd ed., Philadelphia, W. B. Saunders, 1942.
5. BARBER, R. F.: In Therapeutics of Infancy and Childhood, Philadelphia, F. A. Davis, p. 3658, 1942.
6. HOLT, L. E.: Diseases of Infancy and Childhood, 11th ed., New York, D. Appleton-Century, p. 813, 1940.
7. MAHONEY, P. J., and CHAMBERLIN, J. W.: J. Pediat., 17, 772, 1940.
8. KERESZTURI, C.: Am. J. Dis. Child., 59, 1290, 1940.
9. ROSENBLATT, M. S., and WOOLLEY, P. V., JR.: Ann. Surg., 117, 635, 1943.
10. BOWEN, F. H.: Am. J. Obst., 42, 144, 1941.
11. TOMPKINS, P.: J. Am. Med. Assn., 113, 913, 1939.
12. ALTHOFF, F.: Zentralbl. f. Gynäk., 65, 1398, 1941.
13. MARKUS, H.: Zentralbl. f. Chir., 62, 2223, 1935.
14. CRANWELL, D. J.: Rev. d. gynéc. et de chir. abd., Paris, 9, 635, 1905.
15. BONNET, A.: Contribution to the Study of Obstructions of the Vaginal Canal by Transverse Membranes and Their Surgical Treatment, Paris Thesis, 1930.
16. KOFF, A. K.: Contributions to Embryology, No. 140, vol. 24, Carnegie Inst. of Washington, Pub. 443.
17. DOBSZAY, L.: Am. J. Dis. Child., 56, 1280, 1938.
18. CAGNETTO, F.: Riv. ital. di ginec., 22, 209, 1939.

## THE USE OF PENICILLINASE IN CULTURES OF BODY FLUIDS OBTAINED FROM PATIENTS UNDER TREATMENT WITH PENICILLIN\*

BY HARRY F. DOWLING, M.D.

AND

HAROLD L. HIRSH, M.D.

WASHINGTON, D. C.

(From the George Washington Medical Division, Gallinger Municipal Hospital, and the Department of Medicine, George Washington University School of Medicine)

SINCE Abraham and Chain<sup>1</sup> first prepared from *Escherichia coli* a substance which inhibited the action of penicillin on bacteria and which they named penicillinase, many other observers have obtained substances with similar properties from various organisms.<sup>2,4,7,8</sup> It has been suggested that penicillinase might be used in culture media when cultures are obtained from a patient under treatment with penicillin. If sufficient penicillinase were present in the culture medium to inhibit the action of the penicillin contained in the patient's body fluids, then any organisms present should grow without interference.

With this purpose in mind, we investigated the effect of ordinary blood culture medium upon penicillinase.† We found that, when

\* Miss Ruth Mayer and Miss C. Barbara O'Neil rendered technical assistance.

† Penicillinase was supplied by Dr. Harold J. White of the American Cyanamid Co., and by Dr. Charles E. Dutchess of Schenley Laboratories, Inc.

penicillinase was added to veal-infusion broth, and kept at incubator, room, or refrigerator temperature, the penicillinase did not diminish in potency over the course of 4 weeks. Further studies showed that penicillinase, in the concentrations necessary to inhibit the action of the penicillin present in body fluids, did not in itself interfere with the growth of bacteria.

Our next problem was to find the relative rate at which penicillin loses its potency when incubated in broth, alone and with penicillinase. In order to determine this, we added penicillin, in sufficient quantity to make a concentration of 1.25 units per cc., to a flask containing 40 cc. of veal-infusion broth, such as we use routinely for taking blood

**RATE OF DESTRUCTION OF PENICILLIN  
BY VARYING CONCENTRATIONS OF PENICILLINASE  
IN BLOOD CULTURE MEDIUM**

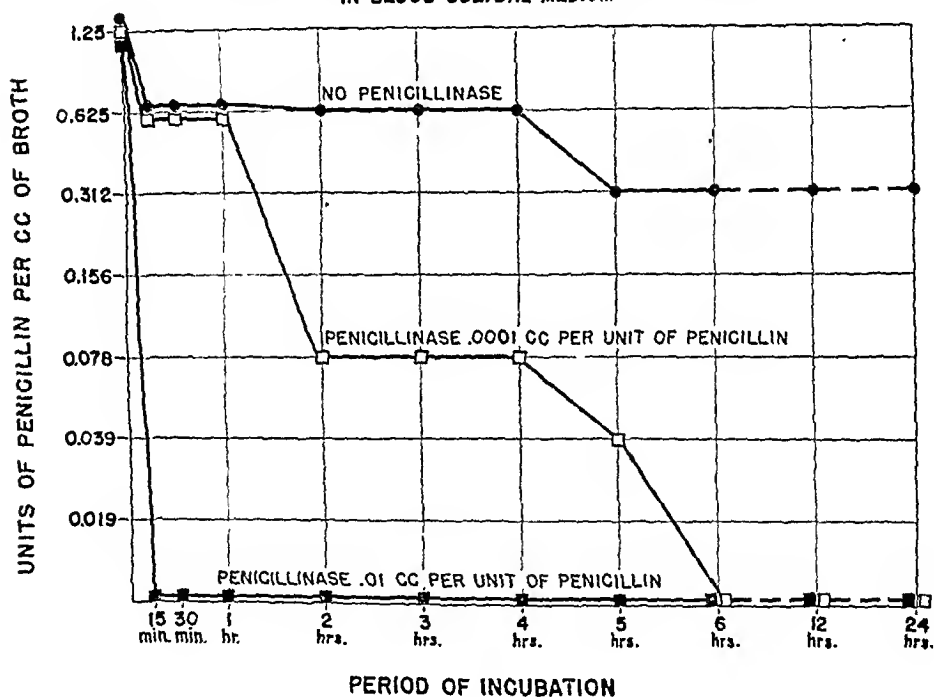


FIG. 1

cultures. This was incubated for 24 hours, along with other flasks containing the same ingredients plus varying amounts of penicillinase. Samples from each flask were removed at frequent intervals and their penicillin content determined immediately by the method of Rammelkamp.<sup>6</sup> Figure 1 shows the result obtained in a typical experiment. In the flask containing no penicillinase, there was only slight diminution in the concentration of the penicillin over the course of 24 hours, while in the flask containing 0.01 cc. of penicillinase per unit of penicillin, no penicillin was detectable after 15 minutes of incubation, when the first sample was taken. When only 0.0001 cc. of penicillinase was used per unit of penicillin, penicillin could still be detected for the first 5 hours, in gradually decreasing concentrations, but not after that time.

TABLE 1.—COMPARATIVE RESULTS OBTAINED, WITH AND WITHOUT THE USE OF PENICILLINASE, IN CULTURES FROM PATIENTS UNDER TREATMENT WITH PENICILLIN

Disease	Etiologic organism	No. of patients	Material cultured	Initial positive culture followed by cultures				
				Positive with or without penicillinase	Negative with or without penicillinase	Negative without penicillinase, positive with penicillinase	Inhibited without penicillinase, positive with penicillinase	Inhibited without penicillinase, negative with penicillinase
Endocarditis	<i>Strep. viridans</i>	6	Blood	8	63	2	4	1
Endocarditis	<i>S. albus</i>	1	Blood	0	0	0	0	0
Endocarditis	<i>S. aureus</i>	1	Blood	0	10	0	0	0
Bacteremia	<i>S. aureus</i>	1	Blood	1	10	0	2	0
Meningitis	Pneumococci—Types 2, 6, 12, 31	5	Spinal fluid	1	23	3	0	0
Meningitis	Pneumococcus—Type 31	1	Blood	1	2	0	0	0
Pneumonia	Pneumococci—Types 4, 8, 12, 12	4	Blood	0	5	0	0	0
Empyema	<i>S. aureus</i>	1	Chest fluid	0	4	0	0	0
Empyema	Pneumococci—Types 1, 2, 4	3	Chest fluid	0	8	3	0	0
Arthritis	<i>Strep. hemolyticus</i>	1	Joint fluid	0	2	0	2	0
Arthritis	<i>S. aureus</i>	1	Joint fluid	0	3	0	1	0
Pyelitis	<i>S. aureus</i>	1	Urine	8	0	0	13	0
	All patients:	26		19	130	14	22	1
				149 (80%)			36 (20%)	

From this and similar experiments we found that penicillin in culture medium, unaccompanied by penicillinase, remained active for 24 hours or longer, and thus inhibited growth of sensitive bacteria during that time. When a sufficient amount of penicillinase was added, it inactivated a therapeutic concentration of penicillin within 15 minutes or less. Insufficient quantities of penicillinase produced no inactivation of penicillin at all, while intermediate amounts of penicillinase produced partial inactivation at first, followed by complete inactivation after variable lengths of time.

We have used penicillinase in veal-infusion broth for culturing body fluids from patients receiving penicillin for various diseases. In each instance a parallel culture was made, using the same medium without penicillinase. In Table 1 are shown the results obtained in 26 patients whose cultures were positive before penicillin therapy was begun. Among the 186 cultures taken on these patients while penicillin was being administered, the results of the cultures taken with penicillinase confirmed the results obtained in those taken without penicillinase in 149 instances (80%). In 19 of these there was growth in both media, and in 130 there was no growth in either. This large number of negative cultures is accounted for by the fact that we continued to take parallel cultures, with and without penicillinase, on several patients long after all clinical evidence of infection had subsided.

In 36 (20%) of the cultures obtained, growth was poor or absent in the medium which lacked penicillinase, while organisms grew well in the parallel culture containing penicillinase. In 14 instances growth was excellent in the penicillinase medium and absent in the other, while in 22 instances growth was excellent in the penicillinase medium and inhibited in the medium lacking penicillinase. This "inhibition" of growth by the penicillin present in the body fluid was manifested in one of two ways: first, by a slowing of growth so that organisms could not be detected until 48 or 72 hours had elapsed, instead of within 24 hours, as had been true before penicillin was administered; or, secondly, by the fact that the bacteria grew sparsely in the fluid medium and not at all when transplanted to blood agar plates.

In only one instance was growth absent in the medium containing penicillinase and present, although the organisms grew sparsely, in the penicillinase-absent medium.

If these results are applied to the number of patients examined rather than to the number of individual cultures taken, the effect of penicillinase is even more striking. There were 26 patients in the group. In 14 (54%) of these, the cultures taken with penicillinase confirmed those taken without penicillinase in every instance. In the case of 8 patients (31%), one or more cultures taken with penicillinase were positive, while cultures taken at the same time without penicillinase were negative. Cultures taken on 4 patients (15%) showed excellent growth in the medium containing penicillinase, while those taken at the same time without penicillinase showed sparse or delayed growth.

Thus in 46% of the patients on whom cultures were taken, the

presence of penicillinase in the medium gave information which was not obtainable or which was delayed or doubtful when the culture was taken without the benefit of penicillinase. Usually, the cultures in which a discrepancy was observed between those taken with and those taken without penicillinase, were the first ones obtained after penicillin therapy was started. We were able to culture the blood from 4 patients with endocarditis and from 1 patient with bacteremia at frequent intervals after therapy with penicillin was begun. Cultures were taken every hour for 6 hours, then at 12 and 24 hours and twice daily for several days thereafter. The results are shown in Table 2.

TABLE 2.—TIME REQUIRED BY PENICILLIN ADMINISTERED THERAPEUTICALLY TO INHIBIT OR PREVENT THE GROWTH OF BACTERIA IN THE BLOOD IN RELATION TO THE PRESENCE OR ABSENCE OF PENICILLINASE IN THE CULTURE MEDIUM

Patient	Disease	Etiologic organism	Time after beginning of penicillin treatment before the penicillin			
			Inhibited growth		Completely prevented growth	
			In medium not containing penicillinase (hrs.)	In medium containing penicillinase (hrs.)	In medium not containing penicillinase (hrs.)	In medium containing penicillinase (hrs.)
R. L.	Endocarditis	<i>Strep. viridans</i>	1	3	9	9
S. T.	Endocarditis	<i>Strep. viridans</i>	1	4	4	5
L. P.	Endocarditis	<i>Strep. viridans</i>	6	30	12	54
J. P.	Endocarditis	<i>S. albus</i>	..	1	1	*
S. T.	Bacteremia	<i>S. aureus</i>	1	4	6	96

\* Not prevented. Growth was complete in each of 6 cultures taken hourly. Patient died 3 hours later.

In 3 patients with *Streptococcus viridans* endocarditis, the cultures taken 9, 5 and 54 hours, respectively, after the initiation of penicillin treatment were the first ones to show no growth in the penicillinase-containing medium. In the parallel set of cultures taken without penicillinase, the penicillin present inhibited the bacteria in such a way that the first negative cultures were obtained at 9, 4 and 12 hours, respectively. Likewise, inhibition of growth was apparent sooner in the cultures taken without penicillinase than in the ones containing penicillinase. All 3 of these patients have made what appears to be a clinical recovery from their endocarditis as a result of penicillin treatment.

In the case of the patient with *Staphylococcus albus* endocarditis, there was no growth in the plain blood culture, but the organisms grew profusely in all of the cultures containing penicillinase, which were taken hourly for 6 hours. Further cultures could not be obtained, as the patient died a short time thereafter.

In the case of the patient with *S. aureus* bacteremia (following an operation for fusion of vertebræ), growth was inhibited within 4 hours and completely prevented within 96 hours after the initiation of treatment. In the parallel cultures without penicillinase, these phenomena took place in the cultures obtained 1 and 6 hours, respectively, after penicillin therapy was begun. This patient recovered from his staphylococcal infection.

It is evident that when penicillin is effective against the organism causing endocarditis or bacteremia, the drug clears the blood stream within a few hours to a few days, and that the rate at which the blood is cleared of bacteria cannot be determined correctly unless penicillinase is used in the culture medium.

Cultures were taken on patients with empyema, meningitis and pneumonia at intervals of 24 to 48 hours after the beginning of penicillin treatment. In the 2 cases of pneumococcic empyema in which cultures of the chest fluid remained positive after the beginning of penicillin treatment, pneumococci were grown from the fluid taken as late as 24 and 72 hours, respectively, after penicillin therapy had been started, while no positive cultures were obtained in the media lacking penicillinase.

Two patients with pneumococcic meningitis continued to show positive cerebrospinal fluid cultures after the beginning of penicillin therapy, in one case for 2 days and in the other for 3 days after treatment had been started. The organisms were cultivated only in the medium containing penicillinase, the cultures in the medium without penicillinase being consistently negative after penicillin was administered.

**Discussion.** When patients are under treatment with the sulfonamides, it has long been the common practice to include para-aminobenzoic acid in the medium used for obtaining cultures from their body fluids. It seems likely that a substance which acts similarly to inhibit penicillin should serve the same purpose when cultures are taken from patients receiving that antibiotic. Numerous investigators have shown that penicillinase possesses such an action, and Harper<sup>3</sup> has used it successfully in culturing surface wounds while they were being treated with local applications of penicillin. We have found that penicillinase can be used to inhibit the action of penicillin in liquid media, and that this method sometimes results in obtaining a positive culture of blood or other body fluid from a patient under treatment with penicillin while the cultures taken at the same time without the use of penicillinase showed no growth, or delayed or inhibited growth.

In a number of cultures the organisms did not grow, regardless of whether penicillinase was used. This was undoubtedly due to the rapidity with which therapeutic doses of penicillin cleared the blood stream and body fluids of susceptible bacteria. In 3 cases of *Streptococcus viridans* endocarditis, for instance, the blood was apparently free of organisms in from 5 to 54 hours after penicillin treatment was started. The important consideration is that one cannot be sure that a particular body fluid has been rendered bacteria-free unless penicillinase is used in the culture medium. We feel, therefore, that it is desirable to use it routinely when cultures are to be taken from patients receiving penicillin.

McQuarrie and Liebmann<sup>5</sup> have devised a method of measuring penicillinase in units. One unit is "that amount of enzyme which, in 11 ml. of pH 7.0 solution containing 50 Oxford units of penicillin,



will destroy in 1 hour at 37° C. an amount of penicillin equal to 57.5% of the penicillin recovered in the control." Recently we have used penicillinase standardized by this method. We recommend that 1 unit of penicillinase be added for each cc. of blood or other body fluid which is to be cultured, except in the case of urine, where 100 units of penicillinase should be used for each cc. of urine.

**Summary and Conclusions.** 1. Penicillinase does not lose its ability to neutralize penicillin when both substances are added to veal-infusion broth and kept at incubator, room or refrigerator temperature for 4 weeks. In the concentrations in which it is used for this purpose, penicillinase has no inhibitory effect upon the growth of bacteria.

2. Among 26 patients from whom parallel cultures were taken, with and without penicillinase, the presence of penicillinase in the culture medium gave information in 12 patients which was not obtainable or which was delayed or doubtful when the culture was taken without benefit of penicillinase.

3. Among 186 specimens of body fluids obtained from patients under treatment with penicillin, cultured in parallel with and without penicillinase in the culture medium, 36 (20%) showed better growth in the medium containing penicillinase.

4. It is recommended that penicillinase be used routinely in cultures of body fluids obtained from patients under treatment with penicillin.

#### REFERENCES

1. ABRAHAM, E. P., and CHAIN, E.: An Enzyme From Bacteria Able to Destroy Penicillin, *Nature*, 146, 837, 1940.
2. BONDI, A., JR., and DIETZ, C. C.: Production of Penicillinase by Bacteria, *Proc. Soc. Exp. Biol. and Med.*, 56, 132, 1944.
3. HARPER, G. J.: Inhibition of Penicillin in Routine Culture Media, *Lancet*, 2, 569, 1943.
4. LIEBMANN, A. J., McQUARRIE, E. B., and PERLSTEIN, D.: A Standard Penicillinase Preparation, *Science*, 100, 527, 1944.
5. McQUARRIE, E. B., and LIEBMANN, A. J.: Studies on Penicillinase, *Arch. Biochem.*, 5, 307, 1944.
6. RAMMELKAMP, C. H.: A Method for Determining the Concentration of Penicillin in Body Fluids and Exudates, *Proc. Soc. Exp. Biol. and Med.*, 51, 95, 1942.
7. UNGAR, J.: Penicillinase from *B. subtilis*, *Nature*, 154, 236, 1944.
8. WHITE, H. J.: Personal communication.

## INCIDENCE OF RESPIRATORY INFECTIONS FOLLOWING ATTACK BY PRIMARY ATYPICAL PNEUMONIA IS UNCHANGED

BY PAUL A. LEMBCKE

INSTRUCTOR IN EPIDEMIOLOGY, PUBLIC HEALTH AND MEDICINE, AND DISTRICT  
STATE HEALTH OFFICER  
AND

LAWRENCE E. YOUNG

INSTRUCTOR IN MEDICINE  
ROCHESTER, NEW YORK.

(From the Department of Medicine of the University of Rochester School of Medicine and Dentistry and the New York State Department of Health, and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals)

DURING August and September 1942, a sudden outbreak of primary atypical pneumonia was experienced by the students and staff of the

University of Rochester School of Medicine and Dentistry and the Strong Memorial Hospital. The clinical and epidemiologic features of this sharply circumscribed epidemic have been presented in an earlier paper.<sup>2</sup>

At the time of the institutional outbreak, a number of cases were also observed in the community at large, and cases of atypical pneumonia were reported at a fairly steady rate during the fall and winter of 1942.

In February 1944, an official of the Rochester Board of Education offered the opinion that persons who had atypical pneumonia in 1942 seemed to be relatively free of respiratory infections during the winter of 1943-1944. This official was in a position to observe accurately the state of health of a large number of individuals, and the suggestion that immunity to other respiratory infections might be produced by the agent of atypical pneumonia was therefore given serious consideration. This observation seemed especially significant in view of the fact that the city had just experienced a large epidemic of influenza A.

It occurred to the authors that if the opinion of the official of the Board of Education could be substantiated by controlled study, and if the etiologic agent of atypical pneumonia could be isolated and propagated, this agent might prove to be an effective antigen for immunization against certain common respiratory infections. This line of thought was in keeping with the suggestion of Kneeland and Smetana<sup>1</sup> that atypical pneumonia might actually increase host resistance to bacterial infection. Furthermore, the remote possibility of immunization against at least one other virus by inoculation of the agent (probably a virus) of atypical pneumonia was indirectly supported by the protection against smallpox afforded by the virus of vaccinia.

The object of this paper is to report the incidence of various types of respiratory illnesses among persons who have had atypical pneumonia as compared with those of similar habitat who have not had this disease.

**Method of Study.** On May 24, 1944, questionnaires were mailed to 150 persons, all of whom were current or former members of the institutional personnel. Replies were received from 114 of these individuals including 9 who had moved to other cities for hospital training or had entered military service. Questionnaires were returned by 33 of the 40 persons who had atypical pneumonia during the August-September outbreak in 1942 and whose illnesses were described in a previous report.<sup>2</sup> In addition, replies were obtained from 6 individuals who had atypical pneumonia subsequent to September 30, 1942. The remaining 75 questionnaires from the control group were returned by those whose names had been selected at random from an alphabetical list published in the annual bulletin of the institution.

Each individual was asked if he had been ill, but not hospitalized, during August or September 1942, and if so, he was asked to state the nature of this illness. In addition each person was asked to give the approximate dates of onset of any of the following illnesses he had had subsequent to September 30, 1942: common cold, sore throat or tonsillitis, bronchitis, influenza, bacterial pneumonia and atypical pneumonia.

All persons questioned were familiar with medical terminology, and in spite

TABLE 1.—INCIDENCE OF RESPIRATORY ILLNESSES AMONG VARIOUS GROUPS OF INSTITUTIONAL PERSONNEL DURING A PERIOD OF 20 MONTHS AFTER AN OUTBREAK OF PRIMARY ATYPICAL PNEUMONIA

Group	Total No. persons in group	No. persons having no respiratory illness	No. persons having 1 or more respiratory illnesses	Number and type of illnesses*						Total No. illnesses
				Common cold	Sore throat or tonsillitis	Bronchitis	Influenza	Bacterial pneumonia	Atypical pneumonia	
A. Persons having atypical pneumonia in Aug. or Sept. 1942	33	2	31	88	14	15	5	1	0	123
B. Persons having atypical pneumonia subsequent to Sept. 30, 1942†	6	2	4	11	0	1	1	1	0	14
C. Persons having other respiratory illnesses during Aug. or Sept. 1942	9	0	9	30	5	6	3	0	0	44
D. Persons having no respiratory illness during Aug. or Sept. 1942 and no atypical pneumonia at any time	66	3	63	191	12	15	14	0	0	232
Total:	114	7	107	320	31	37	23	2	0	413
A. {	...	...	...	1.60	0.25	0.28	0.09	0.02	...	2.24
B. {	...	...	...	1.83	...	0.17	0.17	0.17	...	2.33
C. {	...	...	...	2.00	0.35	0.40	0.20	...	...	2.93
D. {	...	...	...	1.79	0.11	0.14	0.13	...	...	2.17
Av. number of illnesses per person year for all persons under observation‡										

\* These groups are, insofar as possible, mutually exclusive.

† The date of onset of atypical pneumonia in the 6 persons of Group B was between Nov. 1942 and Dec. 1943.

‡ Persons in Group B were under observation for an average period of 12 months; persons in Groups A, C and D for an average period of 20 months.

of the fact that the questionnaire strained their memories, it is believed that the replies were as reliable as could be obtained from any group. Special care was taken not to disclose the purpose of the investigation until it was completed.

**Results.** All individuals included in the study were placed in 1 of 4 groups as indicated in Table 1. Tabulation of the number and types of illnesses experienced by the members of each group between Sept. 30, 1942, and May 24, 1944, makes it apparent that those who had primary atypical pneumonia did not acquire any immunity against other varieties of respiratory infection. It should be pointed out, however, that none of the persons who had atypical pneumonia suffered recurrences of this disease, and none of the 75 persons who were free of respiratory infection in August and September 1942 developed atypical pneumonia during the period of study.

The average number of illnesses per person year is essentially the same for all of the groups. The slightly higher figures for Group C are not significant because of the small number of persons (9) included in this group. As expected, the common cold was the most frequently occurring respiratory infection, and the average person, regardless of group, reported approximately 2 respiratory illnesses per year. It is also of interest that 317 (77%) of the total of 413 infections tabulated began during the 10 cold months, November 1942 to March 1943 and November 1943 to March 1944, while only 96 (23%) occurred during the 10 warmer months included in the study.

**Summary.** 1. The incidence of respiratory illnesses during a period of 20 months following an outbreak of primary atypical pneumonia was found to be the same among 39 persons who had had this disease as among 75 persons who had not experienced this type of infection.

2. It is concluded that primary atypical pneumonia neither confers immunity against nor predisposes to the subsequent development of other common types of respiratory illness.

#### REFERENCES

1. KNEELAND, Y., and SMETANA, H. F.: *Bull. Johns Hopkins Hosp.*, 67, 229, 1940.
2. YOUNG, L. E., STOREY, M., and REDMOND, A. J.: *AM. J. MED. SCI.*, 206, 756, 1943.

## INFECTIOUS MONONUCLEOSIS

### AN ANALYSIS OF 26 CLINICAL AND 340 SUBCLINICAL CASES

BY CAPT. RAY VANDER MEER, M.C., A.U.S.

LT. COL. CHARLES H. LUTTERLOH, M.C., A.U.S.

AND

CAPT. JEAN PILOT, M.C., A.U.S.\*

STATION HOSPITAL, CAMP MCCOY, WISCONSIN

THIS presentation is based upon observations made on a series of cases of infectious mononucleosis at Camp McCoy, Wisconsin, from December 1943 to May 1944. The purpose of the discussion is two-

\* We are indebted to 1st Lt. Emily M. Gray, W.A.C., for valuable assistance in the hematologic studies.

fold: (1) to analyze the clinical picture, which is similar to that of many other infectious diseases, and (2) to raise the question as to the presence of a subclinical form of this disease, the diagnosis of which depends solely upon laboratory evidence.

"Drusenfieber" was the name given by Pfeiffer<sup>38</sup> in 1889 to the syndrome of enlarged cervical glands, fever, enlargement of the liver and spleen, occurring in children. Filatow,<sup>8</sup> a Moscow pediatrician, had described a similar condition in 1885 but had attached no name to it. Pfeiffer's terminology was translated as "glandular fever" and was so described by Williams<sup>37</sup> in 1897. In the 3rd edition of Osler's "Textbook of Medicine,"<sup>19</sup> published in 1897, this description was repeated. In the following years the disease was frequently confused with leukemia, causing much surprise because all patients recovered. In an excellent review Smeall<sup>26</sup> relates that Professor Hall<sup>10</sup> in 1914 presented such a case before the Royal Society of Medicine, and Osler, who was president of the Society, related another case which had caused him considerable embarrassment by recovering completely. Several others reported similar experiences. In 1920 the disease entered its hematologic period. Sprunt and Evans<sup>28</sup> published a paper on "Mononuclear Leukocytosis in Reaction to Acute Infection." They used the term "infectious mononucleosis" and emphasized the pathologic lymphoid cells characteristic of the disease. Longcope<sup>14</sup> in 1922 suggested that glandular fever and infectious mononucleosis were synonymous. Since then this concept has gradually been accepted among American writers.

Paul and Bunnell<sup>20</sup> in 1932 added an important discovery showing that in cases of infectious mononucleosis the blood serum contained an increased concentration of antibodies against sheep erythrocytes. Later refinements were made by Forssman, Bailey and Raffel,<sup>1</sup> and Barret. It was found that serum sickness would give a low positive titer which could be differentiated by special absorption tests using guinea pig kidney and ox blood. The clinical picture had also become better described by this time. A great variety of findings were reported besides those originally accepted by Pfeiffer. Central nervous system phenomena, skin manifestations and even jaundice were found to occur. Some investigators attempted to classify their cases into "types," designating them by their main presenting complaint. Tidy<sup>34</sup> in 1934 distinguished three main types: glandular, anginose and febrile. At a later date others were added, and Sokal<sup>27</sup> in 1943 described the following five types: glandular, abdominal, respiratory, meningeal and asymptomatic. Therefore, over a period of 50 years the concept of acute infectious mononucleosis has become gradually more varied but more inclusive and better understood.

The etiology of this disease is not definitely known. Murray, Webb and Swann<sup>17</sup> in 1926 isolated *Bacterium monocytogenes*, belonging to the group of *Listerella*, from spinal fluid of patients. This organism upon injection into rabbits produced a generalized infection associated with an increased number of typical mononuclear cells. In 1929 Nyfeldt<sup>18</sup> reported the isolation of an organism which she called *Bacterium mono-*

*cytogenes hominis* which also produced a characteristic blood picture upon injection in rabbits. In 1939 the same investigator isolated an organism of the *Listerella* group by blood culture in 5 cases of the disease.<sup>33</sup> McKinlay<sup>16</sup> found that repeated blood cultures from 50 different cases of infectious mononucleosis were all negative emulsions of fresh glandular substances made during the acute stages and injected into monkeys were without effect. However, Wising, repeating the same experiment, produced mild clinical symptoms consisting of lymphadenitis and an increase in the mononuclear cells in the blood. Van den Berghe and Liessens<sup>35</sup> in 1939 were even more successful and produced a positive heterophil titer in a *Macacus* monkey injected with emulsions of biopsied glands.

This disease is rarely if ever fatal. Because of this fact the histopathologic picture is confined to biopsy of glands. Gall and Stout<sup>9</sup> did a study on 10 lymph nodes. They state that there is a specific pathologic picture characterized by: (1) marked proliferative activity of the pulp; (2) focal proliferative activity of clasmatocytes; (3) the presence of large numbers of specific infectious mononucleosis cells.

Sprunt and Evans reported definite lymphoid hyperplasia. Pratt<sup>22</sup> reported a reticulo-endothelial type of hyperplasia. Another investigator, Erf,<sup>7</sup> examined scrapings of the inguinal lymph nodes with the supravital staining method. This study showed small transparent spheres or cysts containing a light yellow colored fluid with actively motile brownish black granules. The granules were comma-shaped, L-shaped or irregular shaped and numbered up to 15 to each cyst. The cyst remained intact for a considerable length of time and could be distinguished long after the lymphocytes and the reticulum cells of the lymph nodes had disintegrated. These bodies were alcohol-soluble and for that reason could not be stained in paraffin-embedded blocks.

This disease, though infectious in nature, is believed to be only mildly contagious. Sporadic cases are the usual manifestation. Minor epidemics and small outbreaks have frequently been reported among university students and military personnel. Terflinger<sup>32</sup> in 1908 reported a small epidemic among adults. The next year Burns<sup>4</sup> reported an epidemic in a children's ward. Burnford<sup>3</sup> in 1918 reported an epidemic among soldiers. In 1930 there were 87 cases in the Falkland Islands. A recent outbreak occurred in 1942 in E. M. S. Hospital in Scotland where it became apparent that the infection was widespread in the surrounding district. Steigman<sup>29</sup> reported 20 cases from the American Red Cross Harvard Field Hospital Unit in 1942. Many other epidemics have been reported.

**Observations.** Over a short period of about 5 months the authors observed a relatively large number of cases of infectious mononucleosis. During the early part of the outbreak there appeared several typical cases which fulfilled the usually accepted criteria for diagnosis. Later the manifestations of the disease became more varied. In an attempt to limit our report to *bona fide* cases and yet to give an inclusive survey of the entire situation, we have classified the cases into four main groups (see Table 1).

TABLE 1.—DATA ON 356 CASES OF INFECTIOUS MONONUCLEOSIS

Group	Total	Typical mononucleosis cells present	Heterophil agglutination titer above the accepted normal 1:56	Clinical picture diagnostic of the disease
I . . .	18	+	+	+
II . . .	8	+	0	+
III . . .	13	+	+	0
IV . . .	327	+	0	0

*Group I.* Typical cases (18). The patients in this group presented a positive clinical picture, showed the presence in the blood smear of the typical mononucleosis cells and had an elevated heterophil agglutination titer above 1:56.

*Group II.* Questionable cases (8). The patients in this group presented a diagnostic clinical picture, varied as it might be, also had the typical mononucleosis cells present, but did not at any time during our observation show an elevated heterophil titer.

*Group III.* Subclinical cases (13). The patients in this group presented no clinical findings and had no history of any acute disease in the preceding 6 months which could have been interpreted as infectious mononucleosis, but typical mononucleosis cells were present and the heterophil agglutination titer was distinctly elevated. These cases were designated as "subclinical cases with positive laboratory evidence."

*Group IV.* Seronegative subclinical cases (327). The patients in this group presented no clinical findings and gave no history of any illness in the preceding 6 months which could be interpreted as infectious mononucleosis. The heterophil agglutination titer at the time of investigation was negative but all patients showed a large number of cells resembling those of infectious mononucleosis. These cases were designated as "seronegative" and are highly questionable subclinical cases with only partially positive laboratory evidence.

**Analysis of Clinical Manifestations in Groups I and II.** Frequently the main presenting complaint of an individual case has been used to designate that case as belonging to a certain type. In our observations, most cases seemed to belong to more than one type and it was difficult to determine which was the chief complaint or the most characteristic finding.

In an attempt to classify our series, we listed 16 of the glandular type, 5 of the respiratory type in which cough and nasal discharge were prominent, 3 of the meningeal type in which headache was so marked that a diagnostic spinal tap was done to rule out meningitis, and 2 of the abdominal type where pain in the abdomen was the main complaint. In an analysis of symptoms the order of frequency of some of the clinical manifestations was determined. Table 2 shows this in detail.

1. *Exanthem.* Eight of our cases showed a very definite skin rash. Two of these were practically indistinguishable from the typical rash seen in measles. A third appeared more like the usual manifestation in early scarlet fever. The skin manifestations of this disease have been described by several authors, including Templeton,<sup>31</sup> Tidy,<sup>34</sup> and

Lyght,<sup>15</sup> as a maculopapular eruption, dark red or light pink in color and varying in size from discrete pin-point to large reddish brown purpuric areas. Other authors mention the rash as being vesicular and even urticarial-like lesions have been reported. Sadusk<sup>24</sup> reported confusing the skin lesions of this disease with those of German measles. Templeton also states that 12 of the 17 cases seen by him were practically indistinguishable from German measles.

TABLE 2.—SUMMARY OF CLINICAL MANIFESTATIONS IN THEIR ORDER OF FREQUENCY

	Cases	%
A. Those occurring in more than 50% of the cases:		
1. Malaise . . . . .	23	88
2. Adenopathy, cervical . . . . .	18	69
3. Temperature above 102° . . . . .	18	69
4. WBC above 11,000 . . . . .	18	69
5. Generalized aching . . . . .	16	61
6. Headache . . . . .	15	57
7. Spiking temperature curve . . . . .	14	53
B. Those occurring in less than 50% of the cases:		
1. Adenopathy, generalized . . . . .	13	50
2. Palpable spleen . . . . .	9	35
3. Cough . . . . .	9	35
4. Rash . . . . .	8	30
5. Chills . . . . .	7	27
6. Photophobia . . . . .	7	27
7. Vomiting . . . . .	5	15
8. Nausea . . . . .	5	15
9. Abdominal pain . . . . .	2	7

The incidence of the skin manifestations seems to vary a great deal with individual outbreaks. In one group only 5% of the patients developed a rash, whereas Templeton at the University of California reported that of a total of 91 cases, 18% of them developed a rash. Sometimes antipyretics, barbiturates had been used during the treatment and therefore the question of possible drug eruption confused the picture. We encountered no drug eruptions as far as we could determine.

2. *Fever.* Twelve cases showed a spiking type of septic temperature with peaks reaching as high as 105. daily. The spiking type of curve was the most characteristic finding of the temperature. Total days of temperature over 99.2° varied from 1 day to 14 and appeared to have no bearing on the height of the titer or blood count manifestations. In a few cases the temperature seemed to subside by crisis. Chills were rare.

3. *Adenopathy.* Whereas adenopathy, especially in the cervical region, was one of the early criteria for the disease, we found 7 cases in this series of 26 which showed no adenopathy, either cervical axillary or inguinal, at any time.

4. *Sore Throat and Organisms.* Most of our patients complained of sore throat and showed marked injection and hyperemia of the nasopharynx. A few showed a whitish gray exudate covering the tonsils. Throat cultures were obtained and direct smears were made. All cultures were negative for the hemolytic streptococcus and only 2 cases showed the presence of fusiform bacilli and spirilla. This is in contrast



to a report by York and Eckley<sup>39</sup> who described an epidemic occurring at Cornell University in 1936 consisting of 24 cases, in which there was a high incidence of hemolytic streptococcus in the throats of both well and ill students. More than 50% of the students routinely observed by the health survey at that time showed a positive culture for hemolytic streptococcus.

5. *Malaise.* During the acute episode malaise was usually a minor symptom. The patients felt surprisingly well even at times when their temperature was above 101°.

6. *Palpable Spleen.* In 8 cases the spleen was palpated. This was always one of the later developments during the course of the disease. We never found it before the 10th day; consequently it was no aid in early diagnosis.

7. *Central Nervous System Involvement.* Severe persistent headache occurred in several cases. No true neck rigidity existed and reflexes remained normal. At times the disease suggested meningitis and on several occasions a spinal tap was performed. Only 2 cases had abnormal findings. One of these showed 12 cells, 6 lymphocytes and 6 neutrophils, and a positive Pandy test. The other showed 12 cells, all lymphocytes, and a negative Pandy. There were no residual findings and the symptomatology consisted of headache and moderate drowsiness.

Several cases of acute infectious mononucleosis with central nervous system involvement have been reported. In 1931 Epstein and Dameshek<sup>6</sup> reported 1 case showing 35 monocytes present in the spinal fluid and having a palpable spleen, generalized adenopathy and a typical blood picture. The significance of the heterophil agglutination test had not yet been discovered at that date. Johansen<sup>12</sup> reported another case which showed 16 monocytes in the spinal fluid with marked neck rigidity, awkward speech, impaired memory, and headache of 2 weeks duration. In 1938 Pietzonka<sup>21</sup> presented 3 cases having nuchal rigidity, severe headache, injected tonsils, sore throat, an enlarged spleen, a heterophil agglutination titer up to 1:64, and 29 monocytes present in the spinal fluid. Schmidt and Nyfeldt<sup>25</sup> in 1938 reported 5 cases which showed up to 26 monocytes and as high as 115 lymphocytes present in the spinal fluid but with few meningeal or cerebral symptoms. Thelander and Shaw<sup>33</sup> in 1941 reported 6 cases of infectious mononucleosis with marked symptoms of cerebrospinal involvement. One case showed a spinal fluid cell count of 630 with 70% lymphocytes.

Landes, Reich and Perlow<sup>13</sup> in 1941 reported a new aspect of the disease. The cerebral involvement was very extensive and the clinical picture was that of an acute ataxia with marked involvement of the cerebellar system. The protein in the spinal fluid was increased to 170 mg. per 100 cc. but the cell count remained below 9 lymphocytes. The heterophil agglutination titer was 1:1024. The overall picture in this case was that of an encephalitis. Zohman and Silverman<sup>40</sup> in 1940 described a case associated with evidence of diffuse lower motor

neuron disease. The patient had complete flaccid paralysis of all four extremities. There were noted fibrillary twitchings of his right arm, no sensory disturbances, no atrophy; however, all deep reflexes were abolished.

8. *Abdominal Pain.* The outstanding symptom occurring in a 27 year old woman was generalized abdominal pain which persisted for 2 days. There was no localized tenderness or muscle spasm. The temperature ranged up to 102°. Nausea and vomiting were her only other complaints. On the 5th day the heterophil titer was elevated up to 1:896. Her convalescence was rapid and she was discharged on the 15th day. Sokal refers to this syndrome as the "abdominal type."

9. *Cough.* Seven of our cases complained of a persistent, racking, non-productive cough, somewhat similar to the cough noted in measles. Chest examination was essentially negative except for occasional moist râles in bases. This symptom usually disappeared within 6 days.

10. *Vomiting.* Vomiting was noted in only 2 cases. It was not in any way significant except that it occurred in the one case where abdominal pain was the main symptom and in the other with severe headache tending to confuse the diagnosis.

11. *Leukocyte Count.* Early in the disease, a marked leukocytosis may occur as high as 35,000 with an increase in the neutrophils in most cases. This is usually followed by leukopenia and an associated rise in the total lymphocyte count. The typical mononucleosis cells were often not present until the total lymphocyte count had increased. We are unable to confirm the statement that the degree of leukopenia was related to the height of the titer.

12. *Kahn Test.* In this entire group there was not a single positive reaction to the Kahn test. This differs from many other reports.

13. *Epidemiology.* Among the 26 cases described in Groups I and II, there were only 3 cases with proved contact, 2 nurses and a laboratory worker. The great majority of Groups III and IV, consisting of 340 cases, came from one unit where contact in barracks may be presumed to have been close.

14. *"Type."* Even though it is difficult to classify the patient who has 4 or 5 complaints into any one type, a superficial grouping was made. We included respiratory, glandular, abdominal and meningeal types. We believe the listing is of some value inasmuch as it stresses the diversity of the clinical symptoms of this disease and helps to suggest the diagnosis in cases in which it would otherwise never be considered.

**Discussion of Groups III and IV.** Early during the outbreak of this disease it was observed that a large number of patients in the hospital with no complaints relative to this disease, had typical mononucleosis cells. For a time these were disregarded as insignificant. However, later the consistency of the findings became disturbing and it was decided that some attempt at evaluation and explanation of the presence of these cells should be made.

It had been observed that several of our clinical cases came from

one particular unit. This unit consisted of 600 men engaged in combat training and in apparent excellent health. Blood smears were obtained from 522 men and 217 (41%) revealed the presence of occasional abnormal cells resembling typical mononucleosis cells. About 47% of 101 cases of this group showed over 5% of these cells present in the differential count. An attempt was made to do heterophil titer determinations on this entire group. Only 74 were obtained and these showed the following results:

TABLE 3.—INCIDENCE OF CASES ACCORDING TO TITER

Titer	No. cases
Negative . . . . .	14
1:7 . . . . .	9
1:14 . . . . .	19
1:28 . . . . .	19
1:56 . . . . .	5
1:112 . . . . .	5
1:224 . . . . .	3

The final results showed the presence of 13 cases with typical cells and a titer above 1:56. These represent the Group III cases. None of them gave a history of illness during the preceding 6 months which could be interpreted as being infectious mononucleosis.

Group IV consists of 314 cases which had only the typical cells without elevated heterophil agglutinations and without clinical findings or a past history of illness suggestive of this disease. It is composed of 110 hospital patients admitted for other complaints and 204 cases from the unit survey. A percentage cell count showed that 226 had less than 5% typical cells present and that 88 varied from 5 to 20%. This group consists of the highly questionable cases in which the diagnosis rests entirely on the blood findings. Similar groups have been reported. The most carefully described is that of Reyersbach and Lenert<sup>23</sup> who, in 1941, studied 16 cases which had no symptoms and no physical findings of any kind and in which the Paul-Bunnell test was uniformly negative. The epidemic occurred in a convalescent home for children with rheumatic fever where leukocyte counts were done at regular intervals as a part of the medical routine, also temperatures and pulse rates were taken 3 times daily. In general, the patients were under close medical observation so that no marked symptomatology could have escaped notice. We were not able to do as thorough a check-up in our cases. A few of this group may have had minor symptoms which were not reported to their dispensaries and for which they were not hospitalized.

As the only criterion of this large group was the presence of the characteristic infectious mononucleosis cell, our attention was focussed on its morphology. The various descriptions present in the literature were carefully reviewed and it was decided that from its appearance the cell could be divided into stages of development. The young cell resembles a normal small lymphocyte except that the small rim of cytoplasm stains a deep and characteristic blue color. The next stage

is a larger cell with an oval or kidney-shaped nucleus and a moderate amount of cytoplasm that stains a homogenous deep blue color. The third stage presents the most easily recognized appearance. The cell is large and the cytoplasm is generous and fragile and tends to spread irregularly on the differential smear. The deep blue cytoplasm is most intense in the periphery and fades toward the nucleus. Wherever the cytoplasm is traumatized in making the smear there tends to be produced a triangular wedge of denser accumulation of deep blue stain. The nucleus is large and may be round, kidney-shaped, or irregularly lobulated and the chromatin is distributed in a lace-like pattern that is unlike lymphocytes or monocytes.

Several authors have suggested that these abnormal cells without the confirmation of an elevated heterophil titer should be regarded as an "irritation" form of lymphocytes which are liberated into the blood stream as a response to a variety of foreign proteins. Warren<sup>36</sup> states that a study of blood smears from a variety of cases, including upper respiratory infections, sinusitis and others showed characteristic mononucleosis cells from 1 to 10% in a differential count. Similar observations have been made by Baldridge,<sup>2</sup> Downey,<sup>5</sup> Stuart and Cunningham.<sup>30</sup> However, 204 cases in our group were in excellent health and the other 110 had no illness in which a foreign protein reaction could be suspected. It is also significant that this group of cases was found at the same time that the clinical cases were most frequent. The correct evaluation of the hematologic findings is as yet not completed.

**Treatment.** The treatment of this disease has been mainly symptomatic. Analgesics and antipyretics are useful as measures to make the patient more comfortable. Hot irrigations in cases of sore throat have been found beneficial. Sulfonamide therapy has been recommended, however, when this was used in our series it proved ineffective. Penicillin was used in 3 cases without beneficial results. Convalescent serum has been highly recommended by some authors but it was not used in this series. Three cases with marked throat ulcerations were treated with repeated small doses of mapharsen. Two of these responded very dramatically, but the third showed negligible results. Bismuth salts intramuscularly have been advocated<sup>11</sup> but were not used in this series. The disease appears to be self-limited, usually presenting no longer than 10 days of acute illness, and for that reason too vigorous therapy seems inadvisable.

**Conclusions.** 1. The outstanding feature of this disease is its protean manifestations which may mimic many other diseases, such as measles, German measles, scarlet fever, meningitis and pneumonia.

2. Early in the disease the laboratory findings are inconclusive and the diagnosis must be made by exclusion. A spiking fever, an exanthem, a non-productive cough, headache, and marked leukocytosis proved to be the most common early findings.

3. Marked leukocytosis up to 35,000 with a high percentage of neutrophils occurred in many cases early in the course of the disease. This was usually followed by a leukopenia with an increase in the

absolute lymphocyte count. The typical mononucleosis cells were present in greatest number when the leukopenia was well established.

4. There appears to be no correlation between the clinical severity of the disease and the height of the titer or the percentage of the mononucleosis cells present.

5. We have no explanation for the large number of subclinical cases which were "seronegative" and which showed only the presence of mononucleosis cells in the blood smear. There is no question that these cells were as typical as any described in the literature. Whether or not their presence is pathognomonic or whether there is such a thing as "irritation phenomena" remains to be answered.

#### REFERENCES

1. BAILEY, G. H., and RAFFEL, S.: *J. Chem. Invest.*, 14, 228, 1935.
2. BALDRIDGE, C. W., ROHNER, F. J., and HANSMANN, G. H.: *Arch. Int. Med.*, 38, 41, 1926.
3. BURNFORD, J.: *Brit. Med. J.*, 2, 50, 1918.
4. BURNS, J. E.: *Arch. Int. Med.*, 4, 118, 1909.
5. DOWNEY, H., and STASNEY, J.: *Folia hæmatol.*, 54, 417, 1936.
6. EPSTEIN, S. H., and DAMESHEK, W.: *New England J. Med.*, 205, 1238, 1931.
7. ERF, L. A.: *J. Mt. Sinai Hosp. (N. Y.)*, 3, 113, 1936.
8. FILATOW, N.: *Vorlesungen acute infectiösen Krankheiten im Kindesalter*, 2nd ed., 1897.
9. GALL, E. A., and STOUT, H. A.: *Am. J. Path.*, 16, 433, 1940.
10. HALL, A. M.: *Proc. Roy. Soc. Med.*, 8, 15, 1914-1915.
11. HOUSER, K. M.: *Penna. Med. J.*, 46, 1173, 1943.
12. JOHANSEN, A. H.: *Acta med. Scandinav.*, 76, 269, 1931.
13. LANDES, R., REICH, J. P., and PERLOW, S.: *J. Am. Med. Assn.*, 116, 2482, 1941.
14. LONGCOPE, W. T.: *Am. J. Med. Sci.*, 164, 781, 1922.
15. LYGT, C. E.: *Journal-Lancet*, 1, 58, 1938.
16. MCKINLAY, C. A.: *J. Am. Med. Assn.*, 105, 761, 1935.
17. MURRAY, E. G. D., WEBB, R. A., and SWANN, M. B. R.: *J. Path. and Bact.*, 29, 407, 1926.
18. NYFELDT, A.: *Compt. rend. Soc. de biol.*, 101, 590, 1929.
19. OSLER, W.: *The Principles and Practice of Medicine*, 3rd ed., p. 345, 1897.
20. PAUL, J. R., and BUNNELL, W. W.: *Am. J. Med. Sci.*, 183, 90, 1932.
21. PIETZONKA, H.: *Arch. f. klin. Med.*, 185, 153, 1939.
22. PRATT, C. L. G.: *Lancet*, 2, 794, 1931.
23. REYERSBACH, G., and LENERT, T. F.: *Am. J. Dis. Child.*, 61, 237, 1941.
24. SADUSK, J. F., JR.: *J. Am. Med. Assn.*, 112, 1682, 1939.
25. SCHMIDT, V., and NYFELDT, A.: *Acta oto-laryngol.*, 26, 680, 1938.
26. SMEALL, J. T.: *Edinburgh Med. J.*, 49, 291, 1942.
27. SOKAL, H. B.: *New York State J. Med.*, 43, 848, 1943.
28. SPRUNT, T. P., and EVANS, F. A.: *Bull. Johns Hopkins Hosp.*, 31, 410, 1920.
29. STEIGMAN, A. J.: *Lancet*, 2, 452, 1942.
30. STUART, C. A., WELCH, H., CUNNINGHAM, J., and BURGESS, A. M.: *Arch. Int. Med.*, 58, 512, 1936.
31. TEMPLETON, H. J., and SUTHERLAND, R. T.: *J. Am. Med. Assn.*, 113, 1215, 1939.
32. TERFLINGER, F. W.: *J. Am. Med. Assn.*, 50, 765, 1908.
33. THELANDER, H. E., and SHAW, E. B.: *Am. J. Dis. Child.*, 61, 1131, 1941.
34. TIDY, H. L.: *Lancet*, 2, 180, 236, 1934.
35. VAN DEN BERGHE, L., and LIESSENS, P.: *Compt. rend. Soc. de biol.*, 130, 279, 1939.
36. WARREN, E. W.: *Am. J. Med. Sci.*, 201, 483, 1941.
37. WILLIAMS, D.: *Lancet*, 1, 160, 1897.
38. WINTROBE, M.: *Clinical Hematology*, pp. 839, 1942. PFEIFFER, E.: *Jahrb. f. Kinderh.*, 29, 257, 1889.
39. YORK, W. H., and ECKLEY, P. W.: *Journal-Lancet*, 57, 15, 1937.
40. ZOHMAN, B. L., and SILVERMAN, E. G.: *Ann. Int. Med.*, 16, 1233, 1942.

# A COMPARISON IN MAN OF SULFATHIAZOLE AND 2-SULFANILYL-3-5 DIHYDROTHIAZOLE (SULFATHIAZOLINE, SULFAHYDROTHIAZOLE)\*

BY HARRISON F. FLIPPIN, M.D.

WARD PHYSICIAN, PHILADELPHIA GENERAL HOSPITAL

JOHN G. REINHOLD, Ph.D.

PRINCIPAL BIOCHEMIST, PHILADELPHIA GENERAL HOSPITAL

LEON SCHWARTZ, M.D.

ASSISTANT WARD PHYSICIAN, PHILADELPHIA GENERAL HOSPITAL

AND

ALBERT H. DOMM, M.D.

ASSISTANT WARD PHYSICIAN, PHILADELPHIA GENERAL HOSPITAL  
PHILADELPHIA, PENNSYLVANIA

(From the Committee on Chemotherapy, Philadelphia General Hospital)

SULFATHIAZOLINE† (2-sulfanilyl-3-5 dihydrothiazole, sulfahydrothiazole), synthesized by Raiziss and Clemence,<sup>5</sup> differs from sulfathiazole by 2 additional hydrogens in the thiazole portion of the molecule. It has been shown by Raiziss, Severac, and Moetsch<sup>6</sup> that the therapeutic effect of sulfathiazoline equaled that of sulfathiazole in experimental pneumococcal and staphylococcal infections in mice and that the drug was readily absorbed from the gastro-intestinal tract of the same species. Further studies by this same group, as well as by Kolmer, Rule, and Groskin,<sup>4</sup> suggested that sulfathiazoline was no more toxic in experimental animals than sulfathiazole.

The present report describes observations dealing with the absorption, excretion, and toxicity of sulfathiazoline in man.

**Fate of a Single Dose.** Ten adult patients, convalescing from various medical conditions and showing no evidence of gastro-intestinal, hepatic, or renal disease, were each given a 3 gm. dose of sulfathiazoline by mouth, shortly after a light breakfast. Drug concentrations in blood and urine were determined by the method of Bratton and Marshall.<sup>1</sup> Within 2 hours the average concentration of free drug in blood was 2.4 mg. per 100 cc. (Table 1), while the highest level reached

TABLE 1.—FATE OF SINGLE ORAL DOSE (3 GM.) OF SULFAHYDROTHIAZOLE  
(AVERAGES OF 10 PATIENTS)

Time (hrs.)	Blood			Urine			Dose excreted (cumulative) (%)
	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Acetylated (%)	Free (mg. per 100 cc.)	Total (mg. per 100 cc.)	Acetylated (%)	
2 . . . . .	2.4	3.1	22.6	27.5	36.6	24.8	3.4
4 . . . . .	3.8	5.8	26.3				
6 . . . . .	2.6	3.7	29.8	106.5	153.5	30.6	20.4
8 . . . . .	2.3	3.5	34.3	82.4	129.4	36.3	49.8
24 . . . . .	1.1	1.8	38.8				

\* This work was aided by a grant from The Abbott Laboratories, Philadelphia, Pa.

† This drug was supplied through the courtesy of Dr. G. W. Raiziss, Director of the Dermatological Research Laboratories, Division of Abbott Laboratories, Philadelphia, Pa.

in any 1 patient at this time was 4 mg. per 100 cc. The concentration of free drug showed little further change and at the end of 4 hours the average concentration was 2.8 mg. per 100 cc., the highest average level observed. Average levels above 2 mg. per 100 cc. were maintained for 8 hours. In similar experiments with sulfathiazole, higher average concentrations prevailed during the first 8 hours following administration of the drug, while at 24 hours comparable levels were observed. An average of 30% of the drug was present in the acetylated form in these patients throughout the 24 hour period.

Excretion of sulfathiazoline in urine (Table 1) was less than that of sulfathiazole<sup>7</sup> under comparable conditions, averaging half of the administered drug within 24 hours, whereas 60 to 90% of sulfathiazole was excreted during this time. During the first 24 hours an average of 31% of drug found in the urine was present as acetylsulfathiazoline.

**Effect of Continued Administration.** Thirty-three adults, suffering from pneumococcic pneumonia, were treated with sulfathiazoline. All patients were given an initial 3 gm. dose by mouth which was repeated in 4 hours, then followed by 1 gm. every 4 hours until the temperature remained normal for 48 hours along with evidence of clinical improvement. The average total dosage of drug was 29 gm. Concentrations of free and total sulfathiazoline in blood were determined in samples collected each morning during the time of drug therapy. The average concentration of free drug was 3.3 mg. per 100 cc., with concentrations ranging from 2 to 5.7 mg. per 100 cc. Again, this is only about three-fifths of the average level attained during sulfathiazole therapy. The concentration of acetylsulfathiazoline averaged 1.5 mg. per 100 cc., or 31% of the total drug present in the blood.

**Toxicity.** Of the 33 patients treated with sulfathiazoline, 8 developed untoward reactions attributed to the drug. Vomiting occurred in 6 patients, being mild in 3, moderate in 2, and in one instance necessitating the discontinuance of the drug. Individual cases of skin rash, hematuria, and neutropenia were observed. Crystals containing sulfathiazoline were observed frequently in the urine of patients. The toxic manifestations of sulfathiazoline appear to be about the same as sulfathiazole in the treatment of pneumonia.<sup>2</sup>

**Therapeutic Action in Pneumonia.** Although the response of the group treated with sulfathiazoline was better than that of much larger groups when sulfathiazole or sulfadiazine were employed, the patients comprising the sulfathiazoline treated group presented mainly moderate or mild illness, while those employed for the evaluation of sulfathiazole<sup>2</sup> and sulfadiazine<sup>3</sup> included pneumonias of all degrees of severity so that direct comparison is misleading. Of far greater significance is the observation that 5 patients showing little or no response to sulfathiazoline, improved promptly following substitution of sulfathiazole or sulfadiazine.

It is our opinion that sulfathiazoline is less efficacious for treatment of pneumonia than sulfonamides currently in use.<sup>3</sup> Our observations were limited to this disease and do not necessarily provide any indication of its effectiveness in other conditions.

**Summary.** 1. Concentrations in blood and excretion in urine are less following oral administration of sulfathiazoline in man than with sulfathiazole in equivalent amounts.

2. The toxic effects observed following sulfathiazoline are comparable with those encountered following sulfathiazole in the treatment of pneumonia patients.

3. Sulfathiazoline appears to be less satisfactory for treatment of pneumococcic pneumonia than sulfathiazole or sulfadiazine.

#### REFERENCES

1. BRATTON, A. C., and MARSHALL, E. K., JR.: A New Coupling Reagent for Sulfanilamide Determination, *J. Biol. Chem.*, 128, 537, 1939.
2. FLIPPIN, H. F., REINHOLD, J. G., and SCHWARTZ, L.: Sulfapyridine and Sulfathiazole Therapy in Pneumococcic Pneumonia, *J. Am. Med. Assn.*, 116, 683, 1941.
3. FLIPPIN, H. F., SCHWARTZ, L., and DOMM, A. H.: Modern Treatment of Pneumococcic Pneumonia, *J. Am. Med. Assn.*, 121, 230, 1943.
4. KOLMER, J. A., RULE, A. M., and GROSKIN, L.: The Pathologic Tissue Changes Produced by Sulfathiazole and Sulfathiazoline in Rabbits, *J. Lab. and Clin. Med.*, 27, 1043, 1942.
5. RAIZISS, G. W., and CLEMENCE, L. W.: 2-Sulfanilyl-Amino-Thiazoline, *J. Am. Chem. Soc.*, 63, 3124, 1941.
6. RAIZISS, G. W., SEVERAC, M., and MOETSCH, J. C.: The Chemotherapeutic Studies of 2-Sulfanilyl-3-5 Dihydrothiazole (Sulfathiazoline). *J. Lab. and Clin. Med.*, 27, 1276, 1942.
7. REINHOLD, J. G., FLIPPIN, H. F., and SCHWARTZ, L.: Observations on the Pharmacology and Toxicology of Sulfathiazole in Man. *AM. J. MED. SCI.*, 199, 393, 1940.

### TREATMENT OF HYPERTHYROIDISM WITH A COMBINATION OF IODINE, THIOUREA IN SMALL DOSES, AND DESICCATED THYROID

BY THADDEUS S. DANOWSKI, M.D.

INSTRUCTOR IN MEDICINE

EVELYN B. MAN, Ph.D.

RESEARCH ASSISTANT IN PSYCHIATRY AND MENTAL HYGIENE (BIOCHEMISTRY)

AND

ALEXANDER W. WINKLER, M.D.

ASSISTANT PROFESSOR OF MEDICINE

NEW HAVEN, CONNECTICUT.

(From the Departments of Internal Medicine and of Psychiatry, Yale University School of Medicine, and the Medical Service of the New Haven Hospital)

THIOURACIL rather than thiourea has commonly been employed in this country for the treatment of hyperthyroidism, largely because thiourea is less effective than thiouracil, gram for gram, in the production of goiters in young rats. A few clinical observations also suggested that it might be less effective in the treatment of hyperthyroidism.<sup>1</sup> Furthermore, thiourea medication occasionally produced a dermatitis and was often associated with an unpleasant odor of the breath.<sup>1,5,10,12,13,14,15,16</sup> Unfortunately thiouracil has proven a somewhat dangerous drug, since its use over prolonged periods produces toxic reactions, especially granulocytopenia, in about 11% of all patients treated with it.<sup>3,4,6,7,12</sup> This fact has led us to reinvestigate the clinical effectiveness and toxicity of thiourea in smaller doses than



those previously employed. Contrary to the prevalent impression, thiourea in these doses has been found to be a highly effective agent in the treatment of most cases of hyperthyroidism. A plan of therapy has been evolved using both iodine and thiourea. Some patients also receive desiccated thyroid.

**Materials and Methods.** Twelve patients with hyperthyroidism,\* some hospitalized and some ambulatory, were first treated with 5 to 15 drops daily of strong solution of iodine, U.S.P. (Table 1). After the remission with iodine therapy had reached its maximum, thiourea was started in doses varying between 0.05 and 0.28 gm. once daily. Two patients for a time received larger amounts, up to 0.80 gm. daily, in divided doses. Those patients whose level of serum precipitable iodine fell below normal received 0.06 gm. of desiccated thyroid daily as well. In some instances iodine medication was later discontinued. Four other patients with hyperthyroidism received thiourea without a preliminary course of iodine administration (Table 2). The diagnosis of hyperthyroidism was based on the usual characteristic clinical features of the disease together with an increased concentration of precipitable iodine in the serum and, usually, an increased basal metabolic rate.<sup>8</sup> Various clinical types of hyperthyroidism were included.

Serum precipitable iodine, basal metabolic rate, body weight, pulse rate, erythrocyte and leukocyte counts, size of the thyroid gland, and general clinical condition were carefully followed throughout the entire course. In a few patients the concentration of thiourea in the ultrafiltrate of serum 12 hours after the ingestion of the daily dose was measured.<sup>2</sup>

**Results.** The results in patients treated with iodine, thiourea, and desiccated thyroid are presented in Table 1, those in patients treated with thiourea alone in Table 2.

(a) *Iodine Administration Alone.* Preliminary iodine medication diminished the severity of the hyperthyroidism for a time in most of the patients in Table 1, but failed to produce a complete and lasting remission. In 2 instances (JH and JO) the disease had become progressively more severe after the initial remission under long-continued iodine therapy. Certain exceptional patients in whom iodine did produce a complete and lasting remission were excluded from the group selected for thiourea therapy.

(b) *Iodine and Thiourea Therapy.* Administration of thiourea as well as iodine resulted in a complete disappearance of the signs of thyroid overactivity and depression of serum precipitable iodine to normal or subnormal in 11 out of 12 instances. Even in the 1 partially refractory case (JO) 800 mg. of thiourea daily produced a distinct drop in the serum precipitable iodine with concomitant clinical improvement. Three cases responded well to only 100 mg. of thiourea daily.

(c) *Iodine, Thiourea, and Thyroid Therapy.* Thiourea medication depressed the serum precipitable iodine below 3 gamma % in 4 patients (Table 1). Levels as low as this are characteristic of myxedema,<sup>17</sup> and are never found in euthyroid subjects. The basal metabolism tended to fall more slowly than the serum precipitable iodine, and so was usually normal when the iodine first fell below the normal range. These 4 patients were then given daily maintenance doses of 0.06 gm. of desiccated thyroid. The concentration of precipitable iodine in

\* We are indebted to Dr. M. Heinemann for the opportunity to follow 3 of these patients.

TABLE 1.—TREATMENT OF HYPERTHYROIDISM WITH IODINE, THIOUREA AND THYROID

Patient	Age	Sex	Daily dose*			Time from start (wks.)	Body weight (kg.)	Pulse rate (per min.)	BMR (%)	Serum pre- cipitable iodine (gamma %)
			Strong solution iodine (drops)	Thiourea (gm.)	Thyroid (gm.)					
BP	26	F				0	49.6	82	+41	15.2
			10			4	50.8	78	+16	9.5
			10			10	50.9	76	+26	12.9
			10	0.10		15	52.0	96		6.0
			10	0.10		19	52.8	76	+ 3	3.7
			10	0.10		23	54.9	64	-14	3.2
			10	0.10	0.06	28	52.1	74	+ 8	5.8
MS	70	F		0.10	0.06	36	50.0	80	+ 1	7.0
						0	46.1	94	+43	8.9
			15			2	46.5	80	+19	6.0
			15	0.28		7	46.2	80	+ 4	5.1
				0.28		12	48.1	84	+10	3.3
				0.28		22	48.6	86	+17	0.6
				0.28	0.06	28	49.2	76	+19	6.5
EB	37	F				0			+14	
			15			8	55.7	96	+ 9	18.9
			5			9	56.2	104	+11	10.9
			5	0.28		14	59.4	82	+12	4.1
			5	0.28		18	59.3	78	- 8	3.8
			5	0.28		22	60.2	72	- 9	4.8
			5	0.28	0.06	32	60.5	86	+ 5	5.1
BG	60	F				0	53.0	84	+37	10.6
			5			2	52.4	70	+ 8	7.0
				0.28		5	54.5	84	+23	
				0.28		9		72		4.1
				0.28		18	55.0	72		1.3
				0.28	0.06	31	55.2	60		4.0
JH	57	M				0			+67	
			5			16	52.2	84†	+55	11.4
			15	0.70±		18	52.2	52	+42	5.1
			15	0.70±		22	57.5	56	- 3	0.9
			15	0.56		24	60.4	60	+ 6	4.5
			15	0.28		28		60	-10	1.6
			Thyroxine studies†							
MK	54	M		0.28	0.06	31	60.1	86	+20	5.9
			15	0.28	0.06	60	61.0	60	+ 6	4.3
			16	0.28		0	64.0	88	+44	9.0
				0.28		1	63.8	76	+33	7.9
				0.28		5	67.2	72	+19	7.6
				0.28		14	67.7	60	+11	5.8
				0.28	0.06	25	68.2	64	+ 9	5.7
AP	26	F		0.28	0.06	31	67.6	64	+19	5.0
						0	53.4	80	+36	10.5
			15			2	52.8	68	+ 1	6.6
			15			6	56.9	84	+17	7.3
			5	0.05		10	56.2	80	+10	8.8
			5	0.10		14	57.4	70	+10	4.5
			3	0.20		21	57.8	60	- 6	2.2
SL	57	F				0			+35	
			5			22	49.9	84	+41	9.8
			5	0.28		25	50.4	86		9.6
			5	0.28		29	49.9	66	- 1	6.8
			5	0.28		39	53.5	82	+ 1	3.0
			15	0.28		0	57.0	50	+28	10.9
			2	0.20		8	58.8	66	- 1	3.4
JO	39	F				38	63.3	70	+13	6.2
			15			0				
			15			75	55.8	100	+85	48.2
			15			78	52.0	94	+80	27.5
			15	0.40±		81	50.8	84	+85	17.2
			15	0.80±		82	50.0	84	+84	14.8
						Thyroidectomy				
PG	37	M				0	60.8	72	+42	22.2
			15			3	62.8	72	+12	7.7
			15	0.28		7	64.4	68	+13	7.1
				0.28		14	64.2	60	-16	4.5
			15			0	74.0	66	+22	10.2
			15	0.10		5	72.4	60	+20	14.1
			15	0.28		11	72.0	100		14.3
EC	53	M	15	0.28		17	69.2	60	+15	12.5
			15			24	67.4	70	+19	6.3

\* During interval ending with the time indicated in the same row. † Auricular fibrillation. ‡ Not reported here.

serum promptly returned to and was maintained at normal levels. In 3 cases (BP, EB, MK) thyroid medication was begun before the serum precipitable iodine had declined below normal.

TABLE 2.—TREATMENT OF HYPERTHYROIDISM WITH THIOUREA ALONE

Patient	Age	Sex	Daily dose* thiourea (gm.)	Time from start (wks.)	Body weight (kg.)	Pulse rate (per min.)	BMR (%)	Serum pre- cipitable iodine (gamma %)
WB	46	M		0	70.8	74	+44	9.5
			0.10	4	69.6	76	+43	8.5
			0.10	7	66.2	52	+19	5.7
KM	58	F		0	74.7	88	+32	10.3
			0.28	3	73.2	58	+15	6.4†
JC	15	M		-2	47.5	128	+16	22.5
				0	45.0	100	+7	15.4
			0.28	1				6.5
			0.28	4	51.4	78	-12	7.4
			0.28	9				7.7
MW†	49	F		-1	60.2	80	+37	19.1
				0	59.2	84	+31	12.0
			0.28	1	58.5	80	+35	12.7
			0.28	3	56.6	80	+17	8.9
			0.28	8	61.4	90	+29	9.1

\* During interval ending with the time indicated in the same row.

† Patient stopped thiourea 6 months later; hyperthyroidism promptly recurred.

‡ Serum iodine 5.5 and BMR -17 after 12 weeks of treatment.

(d) *Thiourea Therapy Alone.* The data from the 4 cases in Table 2 indicate that thiourea alone without preliminary iodine medication may also induce a remission in hyperthyroidism, although it was incomplete in 1 case (MW) after 8 weeks. From Table 1 it is clear that thiourea alone may under some circumstances maintain a remission originally induced by a combination of iodine and thiourea medication (MK), and may even result in a subnormal level of serum precipitable iodine (MS, BG).

(e) *Rate of Response to Thiourea.* In view of the variability of response from case to case it cannot be determined from the limited data in Tables 1 and 2 whether preliminary medication with iodine retards or accelerates the response to thiourea. In 2 cases the response appeared within 1 to 2 weeks; 1 (Table 1, JH) had been receiving iodine for a long time, the other (Table 2, JC) had received none. Other cases in both groups only responded after a considerably longer interval.

(f) *Toxic Reactions.* No change in erythrocyte, leukocyte, or differential count of the blood and no urinary abnormalities developed in any patients. A mild halitosis was common. There were no skin eruptions and no febrile reactions. In 1 subject (KM) 0.28 gm. of thiourea daily occasionally produced nausea and vomiting after 6 months of therapy. In another (JO) there was some nausea while taking 400 to 800 mg. daily, but no vomiting. No distinct change in the size or consistency of the goiter and no change in exophthalmos could be detected in any patient.

**Discussion.** Evidently thiourea in daily doses of 0.100 to 0.280 gm. can produce a satisfactory sustained-remission in cases of hyperthyroidism which have previously been brought into partial remission by iodine medication alone. This fact effectually disposes of any theory that previous treatment of the hyperthyroidism with iodine seriously interferes with the action of thiourea. Cases with toxic adenoma and those with diffuse goiter both respond. On the other hand, it cannot be asserted on the basis of the evidence available that there is any true synergistic action between the two types of treatment, since thiourea alone in the same dosage is at times capable of inducing and maintaining a remission. Further observations bearing on this question are now in progress.

The frequency with which the serum precipitable iodine is depressed below normal during continued thiourea medication proves that hypothyroidism is easily produced. Restoration of the serum precipitable iodine to a normal level with a dose of 0.06 gm. of thyroid daily suggests that the larger doses sometimes advocated<sup>11</sup> may be excessive. The lag in the fall of the basal metabolism behind that of the serum precipitable iodine indicates that thyroid medication should be instituted *before* the basal metabolism has fallen and clinical myxedema has appeared. It might well be sound practice routinely to begin thyroid medication as soon as remission of the hyperthyroidism is well established, and to discontinue it only if signs of toxicity recur. This should be especially important if, as seems likely, progression of exophthalmos and of the goiter is favored by functional hypothyroidism.<sup>9</sup>

No conclusive advantages can at present be claimed for the régime which is described here over the commoner form of treatment with thiouracil alone. On the other hand, it is apparently at least as effective in most instances and has the *a priori* advantage that toxic reactions should be minimized by reliance on small doses. It also provides a preliminary reduction of glandular hyperplasia by iodine medication, which should be a distinct advantage should operative intervention become desirable. It is as yet too early to estimate the permanency of the remission obtained with this régime.

These observations clearly illustrate the high sensitivity of the hyperthyroid human subject to thiourea in comparison with that of the normal experimental animal. The effectiveness of these small doses of thiourea suggests the existence of a peculiar sensitivity or avidity of the hyperthyroid patient for thiourea, particularly in view of its effectiveness in spite of the low concentrations of thiourea in serum 12 hours after the single daily dose (0.4 mg. % or less). Assays of relative goitrogenic potency of different therapeutic agents in the normal animal yield results which cannot be applied directly to the human subject. It may reasonably be considered whether the search for goitrogenic substances of higher and higher specific potency is of comparable importance to the search for compounds producing few idiosyncratic reactions. Whether thiourea in small doses is such a substance can only be established by extensive clinical trial.

**Conclusions.** 1. Small doses of thiourea, 0.10 to 0.28 gm., given once daily, usually produce and maintain a satisfactory remission in patients with hyperthyroidism previously treated with iodine.

2. The serum precipitable iodine is commonly depressed to myxedematous levels if these doses of thiourea are continued for some weeks, even before the basal metabolic rate has fallen to subnormal levels. Desiccated thyroid, 0.06 gm. daily, suffices to restore euthyroid concentrations of serum precipitable iodine.

3. Iodine medication does not inhibit the action of thiourea. Whether it delays or whether it accelerates or synergizes the response to thiourea is as yet uncertain.

4. A therapeutic régime for the medical treatment of hyperthyroidism based on these observations is described.

#### REFERENCES

1. ASTWOOD, E. B.: J. Am. Med. Assn., 122, 78, 1943.
2. DANOWSKI, T. S.: J. Biol. Chem., 152, 201, 1944.
3. GABRILOVE, J. L., and KERT, M. J.: J. Am. Med. Assn., 124, 504, 1944.
4. HALER, D.: Brit. Med. J., 1, 382, 1944.
5. HIMSWORTH, H. P.: Lancet, 2, 465, 1944.
6. KAHN, J., and STOCK, R. P.: J. Am. Med. Assn., 126, 358, 1944.
7. MCGAVACK, R. H., GERL, A. J., VOGEL, M., and SCHWIMMER, D.: J. Clin. Endocrinol., 4, 249, 1944.
8. MAN, E. B., SMIRNOW, A. E., GILDEA, E. F., and PETERS, J. P.: J. Clin. Invest., 21, 773, 1942.
9. MEANS, J. H.: Ann. Int. Med., 19, 567, 1943.
10. NEWCOMB, P. H., and DEANE, E. W.: Lancet, 1, 179, 1944.
11. PALMER, M. V.: Ann. Int. Med., 22, 335, 1945.
12. PASCHKIS, K. E., CANTAROW, A., RAKOFF, A. E., WALKING, A. A., and TOURISH, W. J.: J. Clin. Endocrinol., 4, 179, 1944.
13. RAVENO, W. S.: J. Am. Med. Assn., 126, 153, 1944.
14. Royal Society of Medicine, Lancet 2, 13, 1944.
15. ST. JOHNSON, C. R.: Lancet, 2, 42, 1944.
16. WILLIAMS, R. H., and BISSEL, G.: New England J. Med., 229, 97, 1943.
17. WINKLER, A. W., RIGGS, D. S., and MAN, E. B.: J. Clin. Invest., 24, 732, 1945.

#### PROTEST. A RECORDED PSYCHIATRIC PROGRAM\*†

BY MAJOR ALBERT A. ROSNER, M.C., A.U.S.

AAF REGIONAL HOSPITAL, GREENSBORO, NORTH CAROLINA.

**COMMENTATOR:** This composite recording<sup>1</sup> is made to illustrate some extreme forms of protest adapted and voiced by soldiers in the military service.

\* The neuropsychiatric department of this hospital is preparing a voice-recorded psychiatric library reflecting psychiatric problems encountered in the military service. Recordings are made, with the patient's full knowledge, on a Constant Groove-Speed Reference Recording Machine, using thin, pliable, transparent composition disks, each capable of running for a 1-hour period. (Frank Reiber, Inc., Los Angeles, Calif., U. S. A.)

This is one of a series of recordings on the general subject of failure in the military service. Recorded sequences of original interviews are transcribed, with added commentary, to a single composite disk. Playing time of this disk: 27 minutes.

The recorded library will be available for reference at the Army Medical Library, Washington, D. C.

† Presented phonographically before the Section of Neurology and Psychiatry of the New York Academy of Medicine and The New York Neurological Society, March 13, 1945, at the New York Academy of Medicine, New York City.

As a form of contradiction, protest is a natural and understandable phenomenon. Protest may be conscious, deliberate, and self-assumed, representing legitimate complaint against a disagreeable environmental situation. This is its most apparent and commonplace form. The restrictions of military life and the disciplines imposed by it are very generally unwelcome and are accepted only by compromise. Some, possibly more capable than others of meeting this threat to self-assertion and ego-esteem, absorb this mode of life without demur. Others, more refractory, accept it under protest. Protest, for them, affords natural and self-determined release and serves as an automatic auto-therapeutic mechanism, often an adequate form of cathexis.

Protest may be legitimate or illegitimate, justifiable or reprehensible. Protest may be verbal or non-verbal. It may be wholly behavioristic, and registered as departure from usual or normal behavior. It may be conscious or unconscious. It may be sane or insane. Irrespective of its form, it is usually articulate and recognizable.

Protest is an aggressive rendition that contradicts authority. It is a "combat reaction" due to real conflict between the individual and his environment. Conflict of this type begets symptoms. In these recordings, these symptoms, in a literal sense, are permitted to speak for themselves. Their importance, from the point of view of the military, becomes more and more obvious as one gives ear to the soldier sweating and straining under his burden.

CASE 1. *Protest as dementia praecox.* Interview:

"What was it that brought you to the hospital ten days ago?"

"I had a run-in with an officer. I had on my fatigues and my slippers and was walking down the avenue without a hat, with my hands in my pocket. Naturally the lieutenant stopped me. He called me 'soldier' and I guess I did not like it. I flew off of the handle. He told me to halt, but I did not halt. He held out one arm and tried to stop me. I blew off and went to hit him, but another officer stopped me. Then he and the M. P. had me arrested and I was taken to the Public Relations Building."

"While you were in that building something else happened from what I could gather. Can you tell me what that was?"

"I was walking around in that building and was pretty keyed up, and I saw a picture of the colonel in a desk basket."

"Colonel, who—which colonel?"

"The commanding officer of the Post."

"What did you do?"

"I seized the picture, tore it up, and threw it on the floor."

Later:

"Now what was it, George, that you told me the other day about those fellows in the barracks talking in such an odd and unusual way?"

"Well, they apparently knew something about my past, and practically everything they said reflected on my past. They all seemed to have me involved."

"You seemed to be the center of all of this conversation?"

"Yes, sir, I seemed to be in the middle of it all."

"What is this about a girl that you mentioned before?"

"I think I have seen her here on the field. It seems to have been related to my being arrested and put in the stockade. I have seen her on the field in various automobiles. I thought possibly she was going out with the Commanding Officer of the Post. I thought that the FBI originally was involved in the affair, but now I don't know."

"Now, when you look back upon the whole incident, how does it appear to you?"

"It appears that I had a poor perspective. Things seemed to be out of focus."

CASE 2. *Protest as hysteria.* Interview:

"Now, what is your trouble, James, how long have you been in the hospital?"

(*Breathlessly*) "I don't know how long I have been here. They gave me shots and my whole body got paralyzed and I have been paralyzed ever since."

"Tell me more about it."

"I am weak."

"Why do you breathe so heavily, are you out of breath?"

"I am just weak."

"You seem to be fairly upset about something."

"I am all right."

"Why can't you walk?"

"My legs won't hold me. I fall."

"Do you sleep all right at night?"

"No sir, I don't know why. (*Desperately*) I just can't breathe!"

"How long have you been in the army, James?"

"About two years. I have never been in the hospital before. They gave me shots the other day and I became stiff all over, and I have been like this ever since. First they gave me five shots, and the other day they gave me four, and then something happened."

CASE 3. *Protest as suicide.* (Mental age: 9 years, 2 months.) Interview:

"Ralph, I want you to tell me what it was that brought you to the hospital about a week ago."

"Well, sir, they said I drank iodine."

"Did you take iodine?"

"I don't know, sir—I don't know. I don't understand it."

"Have you been having a pretty tough time of it in the army?"

"Well, sir, I have."

"What has been the trouble?"

"I have been getting headaches."

"Headaches. And you have been worried about something, haven't you?"

"Well, sir, I was worried about the farm. They need me there, sir."

"And you have been concerned about the chickens too?"

"Yes, sir, I was."

"The other day you became all upset about one of the ward-boys and chickens. Do you remember? You were listening to some music, I think, at the time."

"About the records, sir?"

"Yes, tell me about that."

"Oh, them records, I cannot understand them, sir. I don't know—they just boom, boom all day long, sir."

"Are they jazz records?"

"I don't know what kind of records they are. I never heard records like them before."

"Are they symphony records?"

"Yes, I think that is what you call them. They go boom, boom all day long."

"Have you ever heard records like that before?"

"No, sir, I don't like them."

"What about the rooster?"

"Oh, the rooster. I cannot understand the rooster crowing at night here. I never heard that before."

"Why did you get so upset the other day?"

"Well, they would not let me go over to see the chickens."

CASE 4. *Protest as reaction to overseas assignment.* Commentator:

This 20 year old sergeant was brought to the attention of the psychiatric department a week ago, having been brought to the hospital in an ambulance from a downtown cafe. It is stated that while drinking there, he suddenly

felt dizzy and fell to the ground. He was picked up and brought directly to the hospital. This patient, at first, was considered an epileptic. The next day the patient was fully alert and requested to be returned immediately to his group. An investigation of this soldier's army background revealed that he had advanced by series of promotions to a position as Staff Sergeant, and that he was considered a reliable and conscientious non-commissioned officer.

A few hours after leaving the hospital, the patient reported to the Out-patient Department of the Psychiatric Section and stated that he was unable to remain on duty. He appeared to be in an acutely agitated condition. He was admitted directly to the hospital. He stated, on this occasion, that he had failed to give the psychiatrist the whole story during his previous hospital stay.

Interview:

"Now, Gene, I want you to tell me about the situation which brought you to the hospital. I am referring to the first time you came here."

"I was brought here in an ambulance. I don't remember all the details. I fell on the street and I cannot remember all the details. I told one boy that I did not feel very well, then I fell down."

"How were you when you first came to the hospital in the ambulance, or do you remember?"

"All I remember I was all tight inside. My stomach and head was going around. I don't remember everything that happened very well. I remember waking up on the ward."

Later:

"Now, would you say that this nervousness was brought on in any way by the prospect of going overseas?"

"I don't see why it could be because when I came down here I knew I was going overseas. I volunteered to go over."

"You get along well with all the fellows in your outfit, don't you? They think you are a regular fellow, don't they?"

"Yes, sir, that's true. They have a high regard for me."

"And you earned your promotions because of ability, is that not so?"

"Yes, sir, that's true. I did my job pretty well."

"Is this sort of reaction more or less of a surprise to you?"

"Yes, sir, it is."

Later:

"I don't want any discharge, sir. I have been doing my job for two and one-half years."

"When you say you don't want a discharge, what do you mean?"

"Everybody seems to think I am bucking for something."

"Well, who says that you are?"

"Well, I cannot say definitely, but it is what I think. I just want you to know, sir, that I am not a 'goldbricker'."

"Are you afraid?"

"Yes, sir, I am now."

"Of what?"

"Of going overseas."

Commentator: Intravenous sodium amytal is administered to this patient. The tourniquet is applied and needle is inserted in the antecubital vein. Patient is quite agitated throughout the procedure, but cooperates as fully as he is able.

Interview:

"What's the trouble, Gene, why are you so upset?" (*The patient is too agitated to answer. He cries constantly.*)

"Tell me, Gene, why are you so upset?"

"I just want my wife. I want my wife. Where is she? I want her here."

"Would you care to see her in your present state?"

"I want her here. I want her here." (*Voice rises to a wail.*)

Later:

"Have you been crying a great deal in the last few days?"



"No, not very much."

"Did you ever cry like this before in your life?"

"No, sir, I never have."

"Is this a new experience for you, Gene?"

"Yes, sir, it is."

"What makes you worry about your family so?"

"I just don't want to go overseas."

"Why is that, can you tell me?"

"I don't want to go over that's all. I am scared and I am nervous." (*Continues to cry.*)

"Gene, if we can get you over this feeling, do you think you can make a go of it?"

(*With fine show of spirit.*) "I want to do my part!"

CASE 5. *Protest as hysterical dysphonia.* Interview:

"How long has it been, Arnold, since your voice has been this way?"

(*In a harsh whisper.*) "I started last June."

"You mean that you had an attack like this wherein you could not talk above a whisper last June?"

"Yes, it was just like this. I could not talk above a whisper."

"How long did you have trouble with your voice at that time?"

"The attack lasted about four months."

"Then what happened?"

"Then suddenly one day I was talking."

CASE 6. *Protest as hysterical stammer.* Interview:

"Fear, say the word 'fear'."

"F-f-ff-f-f-f-f-f-f . . ." (*Chest heaves with effort.*)

"Take it a little easier. Breathe more easily."

"F-ff-fff-f-f-f-f-f-fr-fr-f . . ."

"Fear."

"F-ff-f-f-f-f-f-f-f-f-f-f-fff-ff-fr-ff-f . . ." (*After repeated efforts, fails to say the word.*)

"How long have you been here on our Section? How many weeks? How many days?"

"T-t-t-t-t-t-t-t-t-t . . ." (*Shakes head from side to side.*)

"Say the word if you can."

"T-t-t-t-t-t-t-t-t-two." (*Explosive utterance.*)

"That's the idea."

*Commentator.* Six cases are presented illustrating within the limits of a 30-minute period, some forms of protest-symptoms encountered in the military service. Three of these cases were recorded directly during psychiatric interview, while 3 were transcribed from previously cut records to the single disc from which this case sequence is presented.

Protest symptoms are herein represented as a series of unconsciously-determined regressive behavior-patterns that appear to contradict the military environment. All symptoms in these patients appeared in the Zone of Interior, following the basic training period. They represent some of the earlier manifestations of failure in the military service.

#### REFERENCE

1. ROSNER, A. A.: Psychiatric Voice Recording in the Military Service, War Med., 6, 38, 1944.

# PROGRESS OF MEDICAL SCIENCE

## GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF  
FRANK B. BLOCK, M.D.  
SURGEON, JEWISH HOSPITAL

AND

DOUGLAS P. MURPHY, M.D.  
ASSISTANT PROFESSOR OF OBSTETRICS AND GYNECOLOGY, UNIVERSITY OF PENNSYLVANIA  
PHILADELPHIA, PA.

---

### UTERINE BLEEDING AND EXTRAGENITAL DISTURBANCES

BY IRVING L. FRANK, A.B., M.D., M.Sc.D.

ASSOCIATE IN OBSTETRICS, GYNECOLOGY AND ENDOCRINOLOGY, JEWISH HOSPITAL  
PHILADELPHIA, PA.

THE causes of prolonged, excessive or frequent uterine bleeding are usually classified as: (a) Organic pelvic diseases, (b) functional endocrine imbalances, (c) systemic disease processes, and (d) blood dyscrasias.<sup>19</sup> The last 2 groups are conceded a relatively minor rôle,<sup>111</sup> and receive serious study only after various hysterostyptics, local procedures and empiric organotherapy have been unavailing.

While this type of classification is practical from a therapeutic standpoint, it leads to certain etiologic misconstructions. It is now abundantly clear that the rhythm of uterine bleeding is the result of the ebb and flow of pituitary and ovarian hormones. Accentuation or prolongation of this bleeding may be associated with a pelvic lesion, yet the organic defect is not, in one sense, an adequate and independent cause for the bleeding. Despite the presence of various organic lesions, the uterus will have cyclic periods of freedom from bleeding. Moreover, benign pelvic lesions in general do not cause bleeding before the menarche nor after the menopause, and not at any time in very many women. Even if excessive bleeding is associated, it is controllable by endocrine therapy, and may be arrested by castration without removal of the lesion itself.<sup>60</sup>

Benign myometrial or adnexal lesions, therefore, can hardly be considered primary factors in uterine bleeding phenomena, although they may frequently increase bleeding by interference with hormonal mechanisms or pelvic dynamics. Such interference may equally well be ascribed to various systemic disturbances which have been found capable of altering the menses even though the pelvic organs remain anatomically normal. A minor pelvic abnormality may be purely incidental, and serve only as a pretext for surgery which could be avoided by proper attention to the general medical status of the woman.

It should be emphasized that endometrial lesions, benign or malignant, may produce arrhythmic bleeding analogous to wound bleeding, which is

entirely independent of the presence or absence of a functioning endocrine mechanism. Conversely, irregular bleeding is almost always due to a lesion of the genital tract epithelia, and prompt inspection and biopsy is demanded.

In the absence of a demonstrable pelvic lesion, the presence of a functional derangement of the endocrine glands is inferred. Having found evidence of a particular type of hormonal imbalance, we carry out an organotherapy that cures only in the sense that insulin cures diabetes. Although the direction of endocrine imbalance may have been demonstrated, we have been content to counterbalance it, without seeking further for its origin. If we exclude the ovarian dysfunctions of the menarche and menopause, and possibly those due to hereditary and congenital factors, there remain far too many instances that are unexplained, unless we impute to the endocrine mechanism a capriciousness that is biologically illogical. Our purposes here are to list the disturbances and diseases of the body that have been reported to be associated with uterine bleeding, and to estimate the frequency and importance of such causes.

**Influence of the Central Nervous System.** Hinsey has reviewed information pertaining to various neurogenital mechanisms.<sup>50</sup> The denervated genital tract in animals continues to carry out cyclic estrus behavior, conception, gestation and labor. After presacral neurectomy, or after accidental transection of the thoracic cord in humans, menstruation retains its cyclic nature and pregnancy is undisturbed. Transplanted endometrium continues to exhibit cyclic growth and bleeding phenomena, and the transplanted ovary continues to produce ova and secrete hormones.

Although the genital mechanism can thus to a large extent act without neuromotor guidance, experimental and clinical data indicate that the menstrual cycle may be modified by extraneous influences acting through one of several neurologic channels. Soon after the *sympathetic fibers to the uterus* are interrupted by presacral neurectomy, or transection of the spinal cord,<sup>60</sup> there occurs uterine engorgement and a short siege of uterine bleeding. The *denervated ovary* exhibits normal follicular development and the presence of dilated perifollicular vessels indicate that the vasodilator sympathetic fibers are unimportant.<sup>50</sup> However, it has been found that intraocular endometrial transplants fail in monkeys that have a thoracic cord transection, presumably because of lowered estrogen levels.<sup>50</sup>

If the *pituitary stalk* is severed, ovulation is impossible in the rabbit, although various types of afferent stimuli from the genital tract are not essential. Farris has recently demonstrated a transient increase in urinary gonadotropin in men and women following sex excitement.<sup>25</sup> *Sympathetic fibers to the pituitary* may also have some importance, since Friedgood and Pincus have shown that the rate of gonadotropin secretion is increased by faradic stimulation of these fibers in rabbits.<sup>50</sup>

Theobald believes that specific vegetative control over genital functions resides in a *hypothalamic center* in the paraventricularis and the supra-opticus,<sup>112</sup> and that menstrual abnormalities in general are reactions of this center transmitted by its nervous connection to the hypophysis. Miller states that the majority of menorrhagias are psychogenic, and that the chemical disturbance is secondary to a psychic factor acting on the endocrine glands.<sup>75</sup>

Many authors have noted the effects of worry, fright, fatigue, nervous shock, sexual excesses and perversions. Miller reports the case of a newlywed who bled several days weekly, apparently because of fear of

coital pain, after treatment of a rigid hymen.<sup>75</sup> An "inconveniently" premature flow is said to occur in brides from fear or excitement.<sup>35</sup> Theobald relates the case of a woman physician, who, having had one child, began to bleed irregularly only during the time when her husband was home from his travels. Fear of pregnancy was found to be the cause.<sup>112</sup> A case of menorrhagia apparently arising to protect a patient from her desire for extramarital relationships is reported.<sup>75</sup>

*Emotional shock* is apt to produce amenorrhea. In 4 such cases arising after a bombing of London, Loeser did endometrial biopsies which Novak found to show endometrium arrested at the phase of the cycle at which the bombing occurred. Presumably there was an emotional interruption of hormone supply.<sup>66</sup> A shock may arrest a normal flow,<sup>35</sup> and continuous heavy bleeding may have a psychic origin.

Allen and Henry studied 100 cases of *personality disorders* and found somewhat characteristic menstrual alterations.<sup>2</sup> In hypomania the flow is more profuse and prolonged. Manic patients show irregularities and occasional amenorrhea. In mild depression no change was noted, while in intense depression there is at first an increase in amount and duration of flow, and later a hypomenorrhea or amenorrhea. Ripley and Papanicolaou noted no clear correlation between the disturbance and the type of menstrual irregularity.<sup>93</sup> In 221 patients with schizophrenia and affective disorders, they observed in general a prolongation of interval with a prolonged flow. In general, the worse the mental disease, the worse the ovarian function. Mosinger and Fiorentini reached similar conclusions, and were able to demonstrate hyperproliferation in some patients.<sup>81</sup>

*Hypnotic suggestion* has been employed to delay the menstrual flow, and to cure an antecedent polymenorrhea.<sup>35</sup> Immersion of the feet in either *hot or cold water* may arrest the flow.<sup>112</sup>

**Physical Agents.** The effects of *light, temperature, pressure* and other physical factors on biologic reactions in general and on pituitary function in particular are well known in the laboratory animal, and are commonly encountered in women. *Change of climate* frequently delays the menstrual flow. The greatest number of menstrual irregularities occur during the *summer months*.<sup>4</sup> Gunn reviewed the evidence for a *lunar influence* and found it inconclusive.<sup>43</sup> Muller studied the influence of the *high altitude* of a resort on the Jungfrauoch and observed menstrual alterations of various types.<sup>82</sup> Many waitresses had to return to lower levels because of severe menorrhagia. A controlled experiment on 70 female rats showed a shortening of the estrus cycle. Muller believes the effect of altitude is largely on the pituitary gland, but he considers the possible effects of *excess ultraviolet radiation, decreased oxygen supply, and the local effects of low atmospheric pressure* on the vessels of the endometrium.

In 50 women *athletes* Nizza found that menstrual disorders occurred only with violent exercise during the flow.<sup>86</sup> Occupations involving *physical effort* led to menstrual irregularities in one-fourth of 2500 previously normal women.<sup>17</sup> Mayer has extensively reviewed the possible ill-effects of *trauma* and he describes several mechanisms. *Psychic trauma* before the mid-cycle may cause premature rupture of the follicle and thus shorten the cycle. Psychic trauma late in the cycle can cause a sudden premature flow, because of the splanchnic pooling of blood and uterine congestion. During the menses a psychic insult may arrest the flow entirely as a result of a sympathetico-adrenal reaction.<sup>69</sup> To this we may add Markee's observation that intraocularly transplanted endometrium will exhibit a secondary hemorrhage in monkeys frightened late in the menstrual period.<sup>68</sup>

Mayer further writes that *abdominal concussion* in the early cycle may also cause premature follicle rupture and advancement of the menses. Premenstrually a corpus luteum hematoma may be produced, with prolonged and excessive bleeding. During the flow itself, a blow to the lower abdomen can cause local endometrial disruption and an increase of bleeding.

*Cerebral trauma*, especially if a basal skull fracture is produced, may result in prolonged amenorrhea, although irregular bleeding may occur. Actual organic damage to the pituitary gland may be the result of local hemorrhage or pressure from edema, and a permanent hypopituitarism may develop. In some cases, Muller believes that the cerebral concussion has acted only as a severe psychic shock, and that the symptoms will regress spontaneously.<sup>82</sup> Hyperestrinism with endometrial hyperplasia and menorrhagia is said to be common after head trauma.<sup>117</sup>

Porcaro reports menorrhagia following exposure to *benzol*, and cites the similar effects of prolonged exposure to *carbon sulphide*, *phosphorus*, *mercury* and *lead*.<sup>33</sup> *Sedormid* or *quinine* may depress platelet production and thus lead to a hemorrhagic diathesis.<sup>77</sup> *Morphine*<sup>112</sup> and *alcohol* addictions lead to amenorrhea and loss of libido. *Ephedrine sulphate* intranasally leads to menorrhagia in occasional patients.<sup>92</sup>

**Diseases of the Endocrine Glands.** Of the primary endocrine disorders, those of the pituitary, the ovaries and the adrenals are most likely to lead to menstrual dysfunction, but the rôle of the other endocrines should not be ignored. *Hypothyroidism* has long been recognized as a cause of excessive uterine bleeding.<sup>19,30,71,113,118</sup> Gardiner-Hill and Smith<sup>33</sup> studied 59 cases of myxedema and found that of the 23 premenopausal cases 18 (78%) had menorrhagia; 15 patients who had had radiation castration never had any gross pelvic lesion, and unrecognized hypothyroidism may have been the actual cause for the bleeding. Waters and Williams point out that basal metabolic rate determinations are unreliable, and in their own series of menorrhagic hypothyroids the readings were from -22 to +5. The latter patient was clinically myxedematous, and tolerated a daily dose of 6 gr. of thyroid, with disappearance of the myxedema and the menorrhagia. The authors conclude that hypothyroidism can occur with a normal basal metabolic rate determination, and they advise clinical evaluation and therapeutic testing with thyroid medication in menorrhagic cases.<sup>119</sup> Blood cholesterol determinations may be misleading.<sup>31</sup> Shute believes that 81 % of his series of functional bleeders were in occult hypothyroidism, curable by thyroid medication. The basal metabolic rates in this series were  $-6 \pm 13$ .<sup>105</sup> This empiric use of small doses of thyroid is widely recommended and practiced. Novak, however, states that "in the overwhelming majority of cases of functional bleeding, no thyroid element appears to be concerned, and thyroid therapy is of no value."<sup>87</sup>

*Hyperthyroidism* frequently leads to diminution of libido, amenorrhea, menstrual irregularities and sterility, although menorrhagia can appear. In 35 patients, Schachter noted 3 cases of severe bleeding, and 24 other patients showed some menstrual irregularity.<sup>99</sup> Russell and Dean report diminution of flow or amenorrhea in most cases, and menorrhagia in only 3%. In severe hyperthyroidism only 27.5% of patients maintained normal cycles.<sup>97</sup>

The thyroid-ovarian relationship may be due to a specific or to a non-specific action on the gonadal cells. Thyroid extract has a direct inhibitory action on the ovaries, and several investigators have shown that thyroxin causes ovarian degeneration.<sup>64</sup> An intermediate action on pitu-

itary cells may be present,<sup>31</sup> and a direct effect on the local metabolism of the endometrium is quite possible.

*Parathyroid disease* has been mentioned as a possible systemic cause for menorrhagia and the use of parathormone, calcium and viosterol is advocated.<sup>19,20,21</sup> More recent studies on the blood clotting mechanism indicate that calcium deficiencies *per se* are unlikely to result in bleeding tendencies, although the association can occur. Albright states, for example, that in steatorrhea vitamin D may be dissolved in the unabsorbed fat and hence hypocalcemia is produced. In addition, the fat-soluble vitamins A and K are also lost, and thus a hemorrhagic diathesis develops.<sup>1</sup> The same picture may result from daily doses of mineral oil, especially in pregnancy.<sup>56</sup>

Aubertin has studied 100 *diabetic women*.<sup>6</sup> Menstrual disorders followed the onset of diabetes, especially in patients near puberty, and in severe and maltreated cases. Insulin therapy frequently corrected the menstrual disorder, which usually was a transitory amenorrhea or a moderate menorrhagia. The possible mechanisms mentioned are: (a) An underlying pituitary disorder, (b) hereditary hypoplasia of islet and genital tissues, and (c) effects secondary to diabetes. Among the latter are included ovarian degeneration due to hyperglycemia (which has been produced in animals), and endometrial malfunction due to faulty glycogen deposition. Aubertin stresses the fact that menstruation is not seriously disturbed in adult diabetics, and disorders are usually corrected by proper insulin therapy.<sup>7</sup> Roulland, following the original work of Vogt, has used insulin non-specifically in patients with dysfunctional bleeding. He states that a short course of treatment with daily doses of 5 to 20 units will work promptly or not at all. The beneficial effect is not due to a pharmacologic or styptic action but may be the result of improved glycogen metabolism in the genital apparatus, or a directly anti-estrogenic effect.<sup>95</sup>

**Infectious Diseases.** Acute infectious diseases are recognized as potential causes, through toxic or debilitating effects on the genital apparatus or endocrine glands. Several months of menorrhagia may follow an acute attack of *mumps oöphoritis*.<sup>10</sup> *Malaria* is a possible cause.<sup>9</sup> Uterine bleeding has been interpreted as an integral part of the *typhoid fever* picture,<sup>123</sup> although amenorrhea is the usual change. Premenstrual *upper respiratory infections* usually delay the flow, and premenstrual *intestinal toxemia* may suppress a flow entirely.<sup>62</sup> Early in the cycle, intestinal toxemia may lead to premature forced rupture of a follicle. Novak states that *pneumonia* and *influenza* may cause transient bleeding, but amenorrhea is more common.<sup>87</sup> In acute suppurative *appendicitis*, Ledoux has noticed toxic ovarian enlargements. He believes that the common factor in all infectious processes is the presence of toxic products which are capable of destroying hormone in the circulating blood, ovarian follicle or stroma.<sup>62</sup>

In chronic infectious diseases, as for example *tuberculosis* and *leprosy*, amenorrhea is common.<sup>26</sup> Menstrual excess may be seen, presumably as the result of increased blood-vessel permeability due to "constitutional depravity."<sup>87</sup> While *syphilis* may cause amenorrhea, Perin reports 2 cases of syphilitic menometrorrhagia, with relief on antiluetic therapy.<sup>89</sup>

**Allergy and the Menstrual Cycle.** Allergic manifestations in general are exaggerated during ovulation, menstruation and the menopause.<sup>39</sup> In young women, the highest average reaction to allergens is obtained on the last day of menstruation.<sup>116</sup> Jahiel believes that reflux tubal menstruation

provides a preparatory intraperitoneal dose of degenerating menstrual fluid. At succeeding menses, the subsequent doses excite anaphylactic liver crises, hepatic colic, asthma and coryza.<sup>55</sup>

In some cases, dysmenorrhea, premenstrual tension and menstrual migraine are the expressions of allergy. Joachimovitz reports a case in which the allergic menorrhagia was aggravated by topical application of the allergen to the cervix, and the menstrual fluid contained large numbers of eosinophils.<sup>58</sup> Rowe has reviewed this subject and relates several cases of uterine bleeding as a result of food allergies.<sup>96</sup> Menstrually recurring purpura of Schönlein-Henoch type is thought to be of anaphylactoid type.<sup>24</sup> Minot noted eosinophilia in 2 cases of menstrual thrombocytopenia purpura and suggested a possible allergic background.<sup>77</sup>

**Blood Dyscrasias.** Failure of normal menstrual discharges to clot has given rise to the widespread impression that some agent of the normal clotting mechanism is lacking, or that an anticoagulant substance is present. Henning states that menstruation is a physiologic hemorrhagic diathesis with thrombopenia and a general tendency to bleed.<sup>48</sup> Glueck and Mirsky showed that menstrual blood does not contain prothrombin, thrombin or fibrinogen.<sup>38</sup> Lozner *et al.* later confirmed this work and pointed out that menstrual blood is like defibrinated blood in its behavior toward thrombin, prothrombin and fibrinogen. No anticoagulants are present but there is an increased fibrinolytic power.<sup>67</sup> The recent studies of Huggins *et al.* are in agreement, and the fibrinolytic enzyme is found to behave like trypsin.<sup>51</sup> These findings suggest that menstrual blood does actually clot within the uterus, the clot undergoing later autolysis and discharge in fluid form. In vigorous uterine bleeding there is no time for fibrinolysis, and clots are discharged externally.

Hence, if the mechanisms which arrest uterine bleeding involve the same processes by which rhexis in general is controlled, we may conclude that any hemorrhagic diathesis may find expression in accentuation and prolongation of the menstrual flow. This is indeed the case, and in a fair proportion of blood dyscrasias, the presenting symptom has been menorrhagia, occasionally with a fatal outcome.<sup>32</sup>

*Secondary anemia* does not in itself give rise to menorrhagia. In 19 cases, Kahn reported normal menses in 12, decrease of flow in 5 and excessive flow in 2. Of 6 cases of *pernicious anemia*, 5 had normal cycles and 1 was hypomenorrheic. *Splenic anemia* was associated with marked menorrhagia.<sup>59</sup>

Haden and Singleton studied 34 cases of *idiopathic hypochromic anemia* (Witts), of which only 1 was a man, and only 4 were postmenopausal women. Menorrhagia (50%) and other menstrual disorders (9%) appeared to be an intrinsic part of the symptom-complex. The authors state that the menstrual disturbance usually disappears as the blood picture returns to normal.<sup>44</sup> In a similar series of 40 women, Gray and Wintrobe report a 67.5% incidence of menorrhagia, which tended to persist despite cure of the anemia. In some patients, heavy bleeding appeared for the first time after the blood picture became normal.<sup>41</sup> Similarly, Hildebrandt reports a 40 year old amenorrheic who began to have normal menses when her "achylic chloranemia" was corrected.<sup>49</sup> A dietary-alimentary deficiency may give rise to this syndrome.<sup>41</sup> The menorrhagia is apt to be misinterpreted as the cause of the anemia.

In 108 cases of *aplastic anemia*, *leukemia* and *purpura*, Buxton found that in 10 women the primary complaint was menorrhagia, and that uterine bleeding was an important secondary symptom in many of the

other cases.<sup>16</sup> Others report bleeding in many leukemia cases and almost invariably in aplastic anemia patients.<sup>59</sup>

A diagnosis of *essential thrombocytopenic purpura* is suggested by severe uterine bleeding at the menarche, especially if there is a history of bleeding from other sites. Lowered platelet level, prolonged bleeding and clot retraction times and decreased capillary resistance (with clinical purpura or ecchymoses) confirm the diagnosis. In many cases, however, the picture is not so clear and recognition is difficult. The patient may have no abnormal bleeding in the past, and a normal menstrual history. Moreover, some patients do not show a lowered platelet level in the beginning of an acute attack<sup>63</sup> nor in a remission.<sup>77</sup> Minot reports 3 patients who at successive menstrual periods had a rapid fall of platelets to very low levels, with menstrual purpuric manifestations, followed by a rapid platelet rise and cessation of abnormal bleeding.<sup>77</sup> More commonly, he states, a patient has a chronic mild depression of platelet level, and bleeds only with further decrease. Sometimes excessive menstrual bleeding is practically the only symptom, and hence platelet counts should be watched in all intractable menorrhagias.<sup>40</sup>

The platelet count falls during the menses.<sup>63,90</sup> Genell showed that this decrease persists until the 11th day of the cycle when there is a sudden rise followed by a gradual recession, and a sudden drop on the 1st day of the subsequent flow. A rise in platelet count also follows parturition, abortion and various surgical procedures, the common factor being resorption of degenerating tissues.<sup>34</sup> Capillary permeability is increased in menstruating women. These findings may reflect an endocrine influence, the exaggeration of which could lead to thrombocytopenic purpura.<sup>77</sup>

Troland and Lee found that spleens removed from these patients yielded an acetone extract which depressed the platelet levels of rabbits. A platelet toxin, "thrombocytopen," may be present,<sup>115</sup> but platelet depression may be a non-specific, and inconstant effect of such extracts.<sup>120</sup> Such a toxin would account for the occasional appearance of purpura in the newborn infants of thrombocytopenic mothers, in the cases collected by Finn.<sup>27</sup>

Many authors report dramatic cures by splenectomy, when other measures have failed.<sup>45,53,85,106</sup> Mettier states that splenectomy is not always satisfactory, since it is dangerous in these patients, and a high percentage of patients have recurrence of symptoms.<sup>72</sup> Stephan, in 1921, demonstrated cessation of hemorrhage after spleen irradiation.<sup>109</sup> Others have used it in various hemorrhagic diseases and in menorrhagias of other cause.<sup>16,21,23,57,104</sup>

Malignant neoplasms, leukemia, septicemia, arsenic, benzene, Roentgen rays and radium may depress platelet production through bone marrow destruction.<sup>72</sup> *Secondary thrombocytopenia* results, possibly associated with menorrhagia. David has described a small epidemic of hemorrhagic purpura, which may be a new syndrome.<sup>22</sup> *Hemophilia* is cited as a cause for uterine bleeding,<sup>9,94</sup> but the existence of this disease in women is doubted, especially since ovarian hormones have been found to be of value in treatment of male hemophiliacs.

In an editorial review, Morhardt discusses Drukker's report of a case of *constitutional thrombopathy* (a form of *pseudohemophilia*).<sup>79</sup> The patient reported had 2 sisters who died of menorrhagia, and 3 other relatives who suffered uterine bleeding, as well as males who showed various bleeding phenomena. The blood findings are a prolonged bleeding time and a normal clotting time, prothrombin time and platelet count. Also men-



tioned are other family groups reported by Von Willebrand, Farber and Minot. Drukker believes that pseudohemophilia may be subdivided into (a) hemorrhagic thrombasthenia of Glanzmann, (b) congenital familial fibrinopenia, and (c) constitutional thrombopathy, as described above. *Idiopathic hypoprothrombinemia*<sup>84</sup> and *hereditary telangiectasis*<sup>8</sup> are rare conditions in which bleeding from various mucous membranes, including the uterine, may be encountered. In the latter condition, bleeding manifestations appear at puberty, before the inherent weakness of blood-vessel walls has led to visible telangiectases.

With associated bleeding phenomena, menorrhagic patients should have a detailed hematologic investigation. Not infrequently, menorrhagia is the isolated manifestation of a hemorrhagic diathesis, and the blood picture may be deceptive at times. Until the correct diagnosis is reached, frequent small blood transfusions will be helpful in most blood dyscrasias.

**Avitaminoses.** Scurvy is uncommon, and most of the reported cases are in men.<sup>70,73</sup> In an unusual series, Ohnell describes 16 female scorbutics in a total of 22 cases, and states that menorrhagia is to be expected in these cases.<sup>88</sup> King asserts that a prescorbutic state is common, and some impairment of physiologic function may be expected before external evidences of deficiency appear.<sup>61</sup> Scorbutic manifestations can be precipitated by infectious processes in individuals with chronic nutritional instability.<sup>73</sup> Evidence of latent scurvy has been found in 20% of autopsies.<sup>124</sup>

Mickelsen *et al.* demonstrated an increased vitamin C level in the plasma at the mid-cycle.<sup>74</sup> Winkler and Seebach, however, found no relationship between the stage of the cycle and the urinary output of ascorbic acid.<sup>122</sup>

Vitamin C has been recommended in treatment of menorrhagia<sup>26,72,83,102</sup> because of its favorable action in sealing off capillary walls and a favorable influence on blood clotting phenomena.<sup>101</sup> The endometrium, like other rapidly growing tissues, may require relatively large amounts of vitamin C. High levels have been found in the substance of the ovaries,<sup>74</sup> the corpus luteum,<sup>11</sup> the pituitary and the adrenal glands.<sup>74,124</sup> Vitamin C deficiency may lead to ovarian dysfunction.<sup>36</sup>

The significance of *vitamin K deficiency* in the etiology of menorrhagia is not clear. Andrus states that avitaminosis K of dietary origin is rare, perhaps because of intestinal synthesis. In intestinal disease, severe diarrheas and adsorption defects a latent K avitaminosis may exist and prothrombin times may be reduced to 60%.<sup>3</sup> Yet this is above the critical bleeding level of 20%. Heilig and Kantiengar point out that liver function is usually depressed during menstruation (by the Quick test), and hence the prothrombin level may fall temporarily.<sup>46</sup> This fall is especially marked in those patients whose prothrombin level is already depressed.

Clinical studies that stress the value of vitamin K are unfortunately lacking in adequate laboratory control.<sup>78,108,114</sup> Relief of dysmenorrhea, disappearance of menstrual clots and abbreviation of flow are reported.<sup>42</sup>

Large doses of vitamin K will not elevate the plasma prothrombin level above normal.<sup>3</sup> While there is no evidence that supererogatory amounts of vitamin K will in any way affect the blood clotting mechanism, Lichtman states that vitamin K possesses coagulant properties independent of the prothrombin mechanism, and may be beneficial in the absence of hypoprothrombinemia.<sup>65</sup> Andrus states that the vitamin is useless unless there is a deficiency,<sup>3</sup> and Cheney concludes that the use of vitamin K to control blood loss from the uterus is without proved success to date.<sup>18</sup>

*Vitamin E deficiency* may not exist in humans, yet there are suggested relationships to the uterine bleeding problem. Wheat germ oil restores the hypoplastic thyroid gland of rats to normal histologic appearance. Vitamin E has been recommended as a potent "anti-estrogen."<sup>105</sup>

The association of menorrhagia, among other possible manifestations of hyperestrinism, and *vitamin B deficiency*, results from the inability of the liver to conjugate and dispose of estrogens unless adequately supplied with B vitamins,<sup>14</sup> especially thiamin and riboflavin.<sup>103</sup> The Biskinds<sup>11-14</sup> have shown that castrate rats with implants of estrone pellets in the spleen, will remain anestrus provided B vitamin intake is adequate. When the rats are placed on a B deficient diet, the estrogen detoxifying function of the liver<sup>54,125</sup> is lost, estrogen escapes into the systemic circulation, and the rats go into estrus.<sup>12</sup> These investigators further point out that many women with clinical avitaminosis B have menorrhagia, premenstrual tension, mastalgia and other symptoms attributable to hyperestrinism. Conversely, patients presenting themselves because of this latter group of symptoms are likely to show lesions of B avitaminosis in addition. Uterine bleeding abates following the use of B complex, even when small myomata are present, and sometimes in the absence of clinical avitaminosis. The deficiency also leads to a depressed basal metabolic rate, which returns to normal on B therapy, but not on thyroid medication alone.<sup>14</sup>

Vitamin B factors, especially thiamin, are low in the American diet. Clinical evidence of deficiency is very common, and subclinical states are probably even more common.<sup>107</sup> Therefore, we are justified in suspecting the B deficiency-hyperestrinemia mechanism in many menorrhagics, and empiric treatment with B complex vitamins, in large doses, may be effective.

Ashworth and Sutton show that a vicious cycle may exist, since an exacerbation of B deficiency lesions occurs with the menstrual cycle, possibly as an estrogen effect.<sup>5</sup> The same authors elsewhere indicate that prolonged B vitamin deficiency may lead to anterior pituitary damage, and thereafter the B deficiency lesions will not completely regress on B vitamin therapy, unless it be supplemented with anterior pituitary extract.<sup>110</sup> Vitamin B deficiency has been shown to cause a decrease of thyrotropic and gonadotropic hormones in rats.

Wiles and Maurer found that *crude liver extract* is useful in some cases of uterine bleeding. This antihemorrhagic factor is present in saponified beef or hog liver fat.<sup>121</sup>

**Visceral Disease.** *Liver diseases*, in general, may lead to menorrhagia. This may be due to release of toxins from degenerating parenchyme, secondary hypoprothrombinemia, secondary thrombocytopenia, or to a loss of the estrogen-detoxifying function. Feminization of cirrhotic men (gynecomastia, fat deposition over the hips and testicular atrophy = Silvestrini-Corda syndrome<sup>23</sup>) is due to an accumulation of the estrogens that cannot be eliminated by a diseased liver. The hormone is largely in free form, and is thus more potent than when conjugated.<sup>12,37</sup> Women with liver disease probably develop hyperestrinism by this same mechanism.

The Quick test reveals a menstrual depression of liver function, especially if interval function is already low.<sup>45</sup> *Acute yellow atrophy* and *cirrhosis* are given as causes for menorrhagia.<sup>9</sup> Morlock and Hall state that in severe liver damage, the platelet count is depressed and prothrombin remains low despite therapy. Hemorrhagic phenomena are seen in 58.8% of cirrhotics and 78% of cases of splenic anemia, in which platelet counts are also reduced.<sup>80</sup>

Roentgen ray to the *spleen* promptly arrests uterine hemorrhage.<sup>109</sup> Among others who confirm the value of this treatment, Dannreuther states that he uses spleen irradiation routinely in juvenile menorrhagia of undetermined origin.<sup>21</sup> Stephan believed that a hyperfunction of the splenic reticulo-endothelial system results in excessive release of a fibrin ferment, and that this is the condition correctible by spleen irradiation.<sup>109</sup> In experiments on rabbits, Ikegami observed an initial decrease in the primordial and growing ovarian follicles, superseded by regrowth and better maturation, and hence he believes that improved ovarian function is a result of spleen irradiation.<sup>52</sup>

Various types of *heart disease*<sup>9,20</sup> especially in decompensated form, with passive pelvic congestion, may cause uterine bleeding. *Chronic nephritis* is listed, as well as *thrombosis* of various abdominal blood-vessels. Heilbronn states that *uterine apoplexy* with sudden hemorrhage is not rare in hypertensive arteriosclerotics, and he reports cases in 2 octogenarian sisters.<sup>46</sup> *Cachectic states* may lead to either amenorrhea or menorrhagia.<sup>15</sup>

**Atypical Bleeding of Physiologic Origin.** "*Implantation sign*" is common, and is due to an escape of blood from maternal sinusoids eroded by the embedding ovum. Sometimes it may persist several days and terminate in heavy bleeding which undermines and aborts the ovum. Rutherford has recently shown that about 60% of normal women have microscopic *ovulatory bleeding* at the mid-cycle.<sup>98</sup> In rare cases, the blood may be grossly visible ("*ovulation sign*," "*little menstruation*").<sup>29,77</sup> *Poly-menorrhea* has been attributed to *multiple ovulation*, on rather tenuous evidence.<sup>76</sup>

**Summary.** The ultimate origin of very many cases of dysfunctional uterine bleeding is not sought out, and we have been willing to accept as causes either minor incidental pelvic lesions or endocrine imbalances, which may be merely intermediate effects. Relief following hormone therapy or curettage does not demonstrate a primary endocrinopathy nor a primary endometrial disease, since both measures are non-specifically helpful, and recurrence of menorrhagia may follow either. Thus, although empiric endocrine therapy or empiric curettage may be effective therapeutic short-cuts, they may only palliate and give a false impression of benefit during the time that a thorough diagnostic search might be under way.

Uterine bleeding has two dangerous implications: cancer and blood loss. The latter will force us to provide prompt therapy, but cancer can be insidious and cannot safely be kept waiting. A reasonable guide to the possible need for early diagnostic curettage is obtained by considering the patient's age, the duration and the type of bleeding. *Metrorrhagia* usually means a neoplastic lesion of the uterine epithelia. The totally irregular bleeding may originate from a totally irregular growth, and curettage-biopsy should not be deferred.

*Menorrhagia*, however, is almost always benign. If it occurs in the course of a systemic disease, the internist may, with reasonable safety, avoid complicating the medical problem by the gynecologic treatment of a condition that may disappear with the general illness (pelvic examination should not be omitted in any case). Tracing menorrhagia to an otherwise subclinical disturbance is a tedious and uncertain process, but on occasion it will suggest cures rather than palliatives, and may often avert unnecessary or fruitless surgical procedures. Accumulating data indicate that uterine bleeding commonly derives from systemic rather than purely local disturbances.

## REFERENCES

- (1.) Albright, F.: *Glandular Physiology and Therapy*, Chicago, Am. Med. Assn., p. 447, 1942. (2.) Allen, E. B., and Henry, G. W.: *Am. J. Psychol.*, 13, 237, 1933. (3.) Andrus, W. de W. H.: *Bull. New York Acad. Med.*, 17, 116, 1941. (4.) Ashley-Montagu, M. F.: *Science*, 89, 290, 1939. (5.) Ashworth, J., and Sutton, D. C.: *Arch. Int. Med.*, 69, 15, 1942. (6.) Aubertin, E.: *Gaz. méd. de France*, 46, 687, 1939.<sup>2</sup> (7.) Aubertin, E.: *Compt. rend. Soc. franç. de gynéc.*, 9, 106, 1939.
- (8.) Barrock, J. J.: *Wisconsin Med. J.*, 43, 805, 1944. (9.) Barton, W. M., and Yates, W. M.: *Symptom Diagnosis*, 4th ed., New York, Appleton-Century, p. 576, 1942. (10.) Beclere, C., and Demange, M.: *Bull. Soc. de gynéc. et d'obst.*, 28, 11, 1939. (11.) Biskind, G. R., and Glick, D.: *J. Biol. Chem.*, 113, 27, 1936. (12.) Biskind, M. S.: *J. Clin. Endocrinol.*, 3, 227, 1943. (13.) Biskind, M. S., and Biskind, G. R.: *Endocrinology*, 31, 109, 1942. (14.) Biskind, M. S., Biskind, G. R., and Biskind, L. H.: *Surg., Gynec. and Obst.*, 78, 49, 1944. (15.) Buxton, C. L.: *Am. J. Obst. and Gynec.*, 42, 502, 1941.
- (16.) Caffier, P.: *Zentralbl. f. Gynäk.*, 61, 1874, 1937. (17.) Capellini, A.: *Difesa sociale*, 19, 1071, 1940. (18.) Cheney, G.: *J. Am. Med. Assn.*, 115, 1082, 1940. (19.) Crossen, H. S., and Crossen, R. J.: *Diseases of Women*, 8th ed., St. Louis, Mosby, pp. 832, 833, 1938. (20.) Curtis, A. H.: *Textbook of Gynecology*, 2nd ed., Phila., Saunders, pp. 95, 290, 291, 1936.
- (21.) Dannreuther, W. T.: in discussion of Phaneuf, L. E., *Am. J. Obst. and Gynec.*, 24, 287, 1932. (22.) David, W.: *Med. Klin.*, 22, 1755, 1926.
- (23.) Edmondson, H. A., Glass, S. J., and Soll, S. N.: *Proc. Soc. Exp. Biol. and Med.*, 42, 97, 1939. (24.) Ellman, P., and Weber, F. P.: *Brit. J. Dermat. and Syph.*, 47, 197, 1935.
- (25.) Farris, E. J.: *Am. J. Obst. and Gynec.*, 48, 200, 1944. (26.) Fauvat, E.: *Ztschr. f. arztl. Fortbild.*, 35, 253, 1938. (27.) Finn, W. F.: *Am. J. Obst. and Gynec.*, 48, 497, 1944. (28.) Fleischmann, Z.: *Wein. med. Wchnschr.*, 78, 131, 1928. (29.) Fluhmann, C. F.: *J. Clin. Endocrinol.*, 1, 202, 1941. (30.) Fluhmann, C. F.: *Glandular Physiology and Therapy*, Chicago, Am. Med. Assn., pp. 213, 215, 1942. (31.) Foster, R. C., and Thornton, M. J.: *Endocrinology*, 24, 383, 1939. (32.) Fraser, E. M. R.: *Lancet*, 2, 1058, 1935.
- (33.) Gardiner-Hill, H., and Smith, J. F.: *Lancet*, 1, 862, 1927. (34.) Genell, S.: *J. Obst. and Gynec. Brit. Emp.*, 43, 1124, 1936. (35.) Gill, M. M.: *Bull. Menninger Clin.*, 7, 6, 1943. (36.) Giroud, A., Ratsimamanga, R., Leblond, C. P., and Rabinowicz, M.: *Gynéc. et obst.*, 34, 424, 1937. (37.) Glass, S. J., Edmondson, H. A., and Soll, S. N.: *Endocrinology*, 27, 749, 1940. (38.) Glueck, H. I., and Mirsky, I. A.: *Am. J. Obst. and Gynec.*, 42, 267, 1941. (39.) Godel, R.: *Presse méd.*, 48, 798, 1940. (40.) Goldburgh, H. L., and Gouley, B. A.: *Am. J. Med. Sci.*, 200, 499, 1940. (41.) Gray, L. A., and Wintrobe, M. M.: *Am. J. Obst. and Gynec.*, 31, 3, 1936. (42.) Gubner, R., and Ungerleider, H. E.: *Indust. Med.*, 13, 301, 1944. (43.) Gunn, D. L.: *Zentralbl. f. Gynäk.*, 62, 1527, 1938.
- (44.) Haden, R. L., and Singleton, J. M.: *Am. J. Obst. and Gynec.*, 26, 330, 1933. (45.) Hartfall, S. S., and Oldfield, C.: *Brit. Med. J.*, 2, 8, 1934. (46.) Heilig, R., and Kantienger, N. L.: *Ann. Indust. Med.*, 16, 538, 1942. (47.) Heilbronn, S.: *München. med. Wchnschr.*, 78, 2077, 1931. (48.) Henning, N.: *Deutsch. med. Wchnschr.*, 50, 1078, 1924. (49.) Hildebrandt, A.: *Arch. f. Gynäk.*, 165, 164, 1938. (50.) Hinsey, J. C.: *Cold Spring Harbor Symposia on Quant. Biol.*, 5, 269, 1937. (51.) Huggins, C., Vail, V. C., and Davis, M. E.: *Am. J. Obst. and Gynec.*, 46, 78, 1943.
- (52.) Ikegami, M.: *Jap. J. Obst. and Gynec.*, 20, 2, 1937. (53.) Israel, S. L., and Mendell, T. H.: *Am. J. Obst. and Gynec.*, 38, 339, 1939. (54.) Israel, S. L., Meranze, D. R., and Johnston, C. G.: *Am. J. Med. Sci.*, 194, 835, 1937.
- (55.) Jahiel, R.: *Arch. d. mal. de l'app. digestif*, 26, 972, 1936. (56.) Javert, C. T., and Macri, C.: *Am. J. Obst. and Gynec.*, 42, 409, 1941. (57.) Jennings, G. H., and Castleden, L. I. M.: *Lancet*, 1, 931, 1939. (58.) Joachimovitz, R.: *Med. Klin.*, 22, 294, 1926.
- (59.) Kahn, M. E.: *J. Am. Med. Assn.*, 99, 1563, 1932. (60.) Karnaky, K. J.: *South. Med. J.*, 33, 1285, 1940. (61.) King, C. G.: *J. Am. Med. Assn.*, 111, 1098, 1938.
- (62.) Ledoux, L. A.: *New Orleans Med. and Surg. J.*, 91, 463, 1939. (63.) Lee, P., and Erickson, B. N.: *J. Lab. and Clin. Med.*, 24, 821, 1939. (64.) Lerman, J.: *Glandular Physiology and Therapy*, Chicago, Am. Med. Assn., p. 407, 1942. (65.) Lichtman, S. S.: *Diseases of the Liver, Gall Bladder and Bile Ducts*, Phila., Lea & Febiger, p. 124, 1942. (66.) Loeser, A. A.: *Lancet*, 1, 518, 1943. (67.) Lozner, E. L., Taylor, Z. E., and Taylor, F. H. L.: *New England J. Med.*, 226, 481, 1942.
- (68.) Markee, J. E.: *Contr. Embryol.*, 28, 223, 1940. (69.) Mayer, A.: *Zentralbl. f. Gynäk.*, 62, 2578, 1938. (70.) McMillan, R. B., and Inglis, J. C.: *Brit. Med. J.*, 2, 233, 1944. (71.) Meares, S. D.: *Med. J. Australia*, 28, 566, 1941. (72.) Mettier,

- S. R.: *J. Am. Med. Assn.*, 108, 83, 1937. (73.) Mettier, S. R., Minot, G. R., and Townsend, W. C.: *J. Am. Med. Assn.*, 95, 1089, 1930. (74.) Mickelsen, O., Drexel, A. L., and Todd, R. L.: *J. Clin. Endocrinol.*, 3, 600, 1943. (75.) Miller, J. A.: *Med. J. and Rec.*, 134, 84, 1931. (76.) Miller, J. A.: *Med. J. and Rec.*, 135, 182, 1932. (77.) Minot, G. R.: *Am. J. Med. Sci.*, 192, 445, 1936. (78.) Miranda, A.: *Hospital, Rio de Janeiro*, 18, 305, 1940. (79.) Morhardt, P. E.: *Presse méd.*, 50, 300, 1942. (80.) Morlock, C. G., and Hall, B. E.: *Arch. Int. Med.*, 72, 69, 1943. (81.) Mosinger, M., and Fiorentini, H.: *Compt. rend. Soc. de biol.*, 132, 156, 1939. (82.) Muller, C.: *Schweiz. med. Wehnschr.*, 68, 397, 1938. (83.) Muller, H.: *Wien. med. Wehnschr.*, 88, 1114, 1938. (84.) Murphy, F. D., and Clark, J. K.: *Am. J. Med. Sci.*, 207, 77, 1944. (85.) Myers, B.: *Lancet*, 1, 764, 1934. (86.) Nizza, M.: *Ginecologia*, 2, 153, 1936. (87.) Novak, E.: *Gynecology and Female Endocrinology*, Boston, Little, Brown, pp. 496, 501, 505, 1941. (88.) Ohnell, H.: *Acta med. Scandinav.*, 68, 176, 1928. (89.) Perin, L.: *Bull. Soc. franc. de dermat. et syph.*, 41, 966, 1934. (90.) Pfeiffer, R., and Hoff: *Zentralbl. f. Gynäk.*, 46, 1765, 1922. (91.) Porcaro, D.: *Ginecologia*, 1, 705, 1935. (92.) Powers, E. G.: *Texas State J. Med.*, 37, 369, 1941. (93.) Ripley, H. S., and Papanicolaou, G. N.: *Am. J. Psychol.*, 98, 567, 1942. (94.) Rongy, A. J., Tamis, H., and Gordon, H.: *Am. J. Obst. and Gynec.*, 31, 300, 1936. (95.) Roulland, M. H.: *Bull. et mém. Soc. de chir. de Paris*, 28, 211, 1936. (96.) Rowe, A. H.: *Am. J. Obst. and Gynec.*, 24, 333, 1932. (97.) Russell, P. M. G., and Dean, E. M.: *Lancet*, 2, 66, 1942. (98.) Rutherford, R. N.: *West. J. Surg.*, 52, 62, 1944. (99.) Schachter, M.: *Paris méd.*, 1, 187, 1936. (100.) Schaefer, W.: *Zentralbl. f. Gynäk.*, 56, 1158, 1932. (101.) Schuchard, W.: *Med. Klin.*, 33, 1522, 1937. (102.) Schumann, E. A.: *Am. J. Obst. and Gynec.*, 38, 1002, 1939. (103.) Segaloff, A., and Segaloff, A.: *Endocrinology*, 34, 346, 1944. (104.) Seitz, L.: *Geburtsh. u. Frauenheilk.*, 2, 516, 1940. (105.) Shute, E.: *Canad. Med. Assn. J.*, 41, 115, 1939. (106.) Snaith, L.: *Lancet*, 2, 684, 1940. (107.) Spies, T. D.: *J. Am. Med. Assn.*, 122, 497, 1943. (108.) Stallworth, W. L.: *Mississippi Doctor*, 17, 678, 1940. (109.) Stephan, R.: *München. med. Wehnschr.*, 68, 746, 1921. (110.) Sutton, D. C., and Ashworth, J.: *J. Lab. and Clin. Med.*, 25, 1188, 1940. (111.) Swinton, N. W., and Blackwell, C. C.: *Surg. Clin. North America*, 21, 865, 1941. (112.) Theobald, G. W.: *Brit. Med. J.*, 1, 1038, 1936. (113.) Thompson, W. O.: *Glandular Physiology and Therapy*, Chicago, Am. Med. Assn., p. 421, 1942. (114.) Titus, P.: *Management of Obstetric Difficulties*, 3rd ed., St. Louis, Mosby, p. 705, 1945. (115.) Troland, C. E., and Lee, F. C.: *J. Am. Med. Assn.*, 111, 221, 1938. (116.) Urbach, E.: *Allergy*, New York, Grune & Stratton, pp. 69, 997, 1943. (117.) von Raiss, D.: *Zentralbl. f. Gynäk.*, 63, 730, 1939. (118.) Walker, J. E.: *J. Med. Assn. Alabama*, 2, 377, 1933. (119.) Waters, W. C., and Williams, G. A.: *Am. J. Obst. and Gynec.*, 23, 489, 1932. (120.) Watson, G. M.: *Brit. Med. J.*, 1, 704, 1941. (121.) Wiles, H. O., and Maurer, S.: *Science*, 89, 293, 1939. (122.) Winkler, H., and Seebach, W.: *Monatschr. f. Geburtsh. u. Gynäk.*, 108, 67, 1938. (123.) Wofford, C. P., Calder, D. G., and Fetter, F.: *J. Lab. and Clin. Med.*, 24, 260, 1938. (124.) Yavorsky, M., Almaden, P., and King, C. G.: *J. Biol. Chem.*, 106, 525, 1934. (125.) Zondek, B.: *Lancet*, 2, 356, 1934.

## PEDIATRICS

UNDER THE CHARGE OF

IRVING J. WOLMAN, M.D.

SURGEON (RESERVE), UNITED STATES PUBLIC HEALTH SERVICE

## CONGENITAL HEMOLYTIC ANEMIA: A REVIEW OF PROGRESS

By IRVING J. WOLMAN

SURGEON (R), U.S.P.H.S. HOSPITAL, SHEEPSHEAD BAY, BROOKLYN 29, N. Y.

THE past few years have witnessed much clinical research on the hematology of congenital hemolytic anemia. Enough progress has been achieved in our understanding of the pathogenesis of this peculiar disorder to warrant the preparation of a Review at this time, even though none of the new information gathered can be characterized as highly sensa-

tional. The various distinctive features to this disorder will be discussed *serialim*, with the comments on each feature extracted from those reports which have emphasized that feature in most detail.

The name of the disease has many synonyms as, for example, chronic hereditary hemolytic jaundice, familial hemolytic jaundice (or *icterus*), familial (or *hereditary*, or *congenital*) hemolytic anemia, familial acholuric jaundice, hemolytic ictero-anemia, congenital spherocytic anemia, splenomegalic icterus of Hayem, Minkowski-Chauffard disease. Exactly which designation one wishes to use is largely a matter of taste, since all have attained authoritative recognition in this or foreign countries. The name selected for use here was adopted largely because Blackfan, Diamond and Leister chose it for their new and definitive "Atlas of the Blood in Children."<sup>5</sup>

**Criteria for Diagnosis.** All suspected cases, according to Haden,<sup>22c</sup> ought to receive certain special clinical laboratory studies to establish the correctness of the diagnosis and to rule out other conflicting kinds of hemolytic anemia. Spherocytosis should be established by measuring the mean diameter and thickness of the red cells. Both plasma and urine should be free from hemoglobin (in this disorder, even in the most active stages, hemoglobinemia and hemoglobinuria are never present, because the red cells are being destroyed in the spleen, not in the circulation). Hemolysins must be absent from the plasma (hemolysins are occasionally demonstrable in other types of hemolytic anemia; splenectomy will not effect relief if the symptoms are due to such hemolysins). Auto-agglutination of the red cells never coexists with spherocytosis. (In acquired hemolytic icterus the erythrocytes not infrequently exhibit this phenomenon.) The quality of the stroma in spherocytes is not defective (in some anemias, such as sickle-cell anemia and idiopathic hemolytic anemia, the stroma is abnormally weak, as evidenced by bizarre shapes or a tendency for rapid spontaneous lysis of the cells when the blood remains in a test tube outside the body). In Haden's opinion the abnormality lies in the shape of the cell. The stroma is normal, and the hemoglobin unaltered, so that the rounded cell functions as well as a biconcave disk as long as it remains in the circulation. For this reason splenectomy, though it has no influence on the spherocytosis or the increased hypertonic fragility which persist though to a lesser degree than before operation, will relieve all symptoms. The increased fragility in hypotonic salt solutions in congenital hemolytic anemia is dependent upon the spherocytosis, though the conditions are not necessarily or always parallel. Spherocytosis, at times, may be present without an increase in hypotonic fragility, seemingly due to some qualitative hardening of the stroma. Conversely there are rare cases in which the red cells have an apparently normal shape but their fragility is greatly increased. Haden justified these conclusions by his observations of 21 patients. In every instance splenectomy was followed by quick disappearance of the anemia and reticulocytosis and the content of bilirubin in the plasma returned to normal.

Dacie<sup>10b</sup> proposed the following criteria as essential to the making of a diagnosis in suspected cases: an anemia of hemolytic type, spherocytosis, an increased susceptibility of the red cells to hemolysis by hypotonic saline, an abnormal tendency of the blood to lysis *in vitro* on incubation at 37° C., and splenomegaly in which engorgement with blood is the outstanding feature. A history of recurrent anemia or jaundice over a period of years and a positive family history are confirmatory, though their absence does not exclude the diagnosis.

**Clinical Features.** *Inheritance.* Meulengracht's<sup>34</sup> 1921 study of 7 Stockholm families established that congenital hemolytic anemia is inherited as a dominant Mendelian character. Such anomalies are transmitted through the affected parent; with 50% of the siblings exhibiting the trait; normal members of an affected family cannot pass it on. A number of other geneologic studies since that of Meulengracht (*e. g.*, that of Debré *et al.*<sup>14</sup>) confirm the accuracy of this theory of the mode of transmission. Race<sup>37</sup> reëvaluated the manner of inheritance by examining blood specimens from 183 members of 26 families in which at least 1 member had the disease. He found the general pattern to be as demonstrated by Meulengracht, except for 2 deviations from the expected trend. The expected ratio of 1 sound to 1 abnormal offspring was not exactly met, and in occasional families the disorder seemed to have skipped a generation. As an explanation for the diminished ratio he pointed to the abnormally high miscarriage and infant mortality rates found in the jaundiced branches of these families, and suggested that there probably was a disproportionate number of positive inheritors among the dead children. He postulated also that the disorder-bearing gene exhibits a lack of full penetrance. Interestingly, in 3 families only 1 child was jaundiced, with parents and all other members having no demonstrable blood abnormality. These may have been instances belonging to the interesting minor group of "acquired" or non-inherited hemolytic anemia.

*Special Manifestations in Infancy.* Abt<sup>1</sup> reviewed the literature on the symptomatology in infancy, and described the progress of 3 cases personally observed. He found a total of 10 recorded instances in which symptoms had shown themselves by 4 months of age. The onset may either be insidious, or appear with terrifying suddenness to terminate acutely in death as with 1 of Diamond's<sup>16</sup> infants. When the illness is first manifested in early infancy, jaundice may be entirely absent, even though there is indisputable evidence of a considerable increase in destruction of blood. Jaundice varies strikingly from time to time and is most marked in a remission following a crisis. The enlarged spleen may extend below the umbilicus and completely fill the left flank. The liver may also show considerable enlargement. Both spleen and liver are usually firm. Cardiac murmurs, probably of "hemic" nature due to anemia, are occasionally noted.

Anemia is always one of the most striking features of the disease in young infants, and may be severe. In 1 of Abt's cases the number of red cells fell to 790,000 per c.mm., and the hemoglobin content similarly diminished. Bilirubinemia is always present: the icteric index is increased, and the indirect van den Bergh reaction is positive. The morphology and fragility of the red cells are the same as with adults, though there seems to be a greater tendency for atypical macrocytic red cells to be free in the circulation. Smears of the bone marrow obtained by sternal puncture reveal an increase in the number of nucleated red cells. In place of the normal 15%, 50% or over have been noted.

The sudden appearance of a hemolytic crisis is usually the first indication that the infant's blood is not normal. First come prodromal symptoms, such as lassitude, lack of appetite and fretfulness, followed promptly by deepened jaundice and increased anemia. The spleen enlarges and the urine becomes dark. Abdominal symptoms are not prominent. Crises are occasionally initiated by febrile attacks; all the symptoms become magnified, and the infant may be extremely prostrated. Anemia is most severe when fever accompanies the crisis. Periodicity in the occurrence

of these hemolytic crises is the rule. The interval between crises varies considerably. Urobilinuria becomes prominent, especially after a crisis. The stools are normal but occasionally dark. Acholia is never present. Hemoglobinuria is rare; it occurred with 1 of Abt's infants during a crisis.

*Special Manifestations in Childhood.* During childhood the disease exhibits more extreme deviations from its typical course than after maturity. This tendency has been emphasized especially by Diamond,<sup>16</sup> who showed clearly that congenital hemolytic anemia, once its presence in childhood has become manifest, often fails to progress in as benign a fashion as later in adult life. These variations from the usual course consist of more profound anemia, interference with proper skeletal growth, and cardiac enlargement with or without decompensation. Diamond comments that the saying, "adults with the disease are more jaundiced than sick," needs to be reversed to read: "children, and especially infants, with this condition are more sick than jaundiced." The younger the patient at the time of the first crisis of hemolysis, the more severe the disturbance tends to become. The anemia is generally more profound; the cells show much more tendency to variation in shape; the reticulocytes may rise to tremendous percentages, as in 1 case where they numbered about 90 % of all the red cells; the fragility test may show beginning hemolysis with normal isotonic saline solutions. The spleen may become so enlarged as to fill the whole left side of the abdomen. Death may occur during an attack, even during the first, for the bone marrow of the young does not have as great an emergency store of red cells; a hemoclastic crisis may be quickly followed by all the symptoms of acute and fatal hemorrhage.

As the child passes through succeeding attacks of hemolysis with jaundice and anemia, his heart enlarges, his valves dilate and become insufficient, and cardiac decompensation may take place. Growth of his skeletal structures is interfered with; not only is stature small but the centers of ossification delay in appearance. The bones tend to become wider, with thinning cortex, in an effort to keep up maximum production of red cells. Some children have seemed to be mentally retarded. In unoperated cases continued hyperbilirubinemia may lead to the production of gall stones with subsequent danger from biliary obstruction. Early splenectomy for the infant or child with active symptoms of congenital hemolytic anemia is therefore strongly advisable, and may be necessary as a life-saving measure.

*Gall Stones.* An instance of gall stones in a 3 year old child has been reported by Gairdner.<sup>19</sup> The preoperative diagnosis was based upon a history of hemolytic anemia, an acute attack of obstructive jaundice, and Roentgen ray demonstration of a shadow suggestive of stone in the region of the gall bladder. On reviewing the literature he found that few cases of gall stones, cholecystitis or common duct obstruction by soft masses of bile pigment have been recorded, although with adults having the disease one of the prominent and most common difficulties is the propensity to biliary tract complications.

*Bones.* Bone changes are almost never seen in congenital hemolytic anemia.<sup>45</sup> Cooper,<sup>6</sup> however, after citing a few similar instances from the older literature, described a family in which 2 affected children had the mongoloid facies and the thickening and vertical striation of the skull-cap bones so often deemed characteristic of Cooley's erythroblastic anemia. He pointed out that these skull changes are occasionally seen also in that third form of chronic congenital hemolytic anemia—sickle-cell anemia. Diamond,<sup>16</sup> as already mentioned, had previously pointed out that in the



3 varieties of congenital hemolytic anemia there is marked thinning of the cortices of the bones of the extremities with increase of the medullary portions due to hypertrophy of the medullary substance.

*Acute Crises.* The crises which come on abruptly for no discoverable reason can be very serious and even lethal.<sup>1,16,23,36</sup> In fact, Curtis, Doan and Wiseman<sup>8</sup> several times with adult patients have had to resort to emergency splenectomy as a life-saving measure because of the severity of a hemolytic episode. Since one hemolytic episode is usually followed by others, McLaughlin<sup>31</sup> recommends a splenectomy for every patient who has experienced one such episode.

Outbreaks of hemolytic crises which break out within a family circle have been referred to by a number of authors.<sup>12,37</sup> Dedichek<sup>15</sup> reported 4 instances of acute crises in 1 family and 9 instances in a second family, each such outbreak lasting a month. Scott<sup>39</sup> has described how within an 18 day interval 4 affected brothers and sisters each experienced a crisis. Damashek<sup>12</sup> discussed 3 children in the same household—2 brothers and a cousin—who became successively ill within 10 days with crises which necessitated emergency splenectomy.

The cause of these crises is shrouded in the same obscurity which conceals knowledge of the cause of any individual attack. Dedichek suspected that his cases were due to a "grippe" infection. The parents of Scott's cases were convinced that emotional sympathy played a large part with the latter 3 of the 4 children. Damashek hypothesized that the crises developed because of some alteration outside the bone marrow affected perhaps by splenic activation which in turn had been provoked by some environmental factor.

All authors agree that the only satisfactory treatment lies in splenectomy. Liver, iron and other medicaments are of no help. Following splenectomy, if the diagnosis is correct, the reticulocyte count returns to normal, and the icterus disappears, because blood destruction no longer takes place.<sup>36</sup> The spherocytosis persists, however.

The surgical treatment has been well discussed by McLaughlin, Sharpe and Cunningham,<sup>32</sup> in their careful report on 29 typical cases in 12 of which the spleen was removed successfully. For those individuals having a sub-clinical disturbance with few or no symptoms an operation is not recommended. The youngest patient of McLaughlin *et al.* was 5 years old, but Bell<sup>2</sup> operated successfully on a 15 month's old child, and Haden<sup>22d</sup> refers to an infant who was operated on at 4 months when weighing only 7 pounds, with complete recovery from symptoms.

Gripwall<sup>21</sup> described the crises of congenital hemolytic anemia as being: (1) thermic, (2) abdominal or (3) essential blood crises. Lowe<sup>30</sup> commented that the mechanism of the so-called thermic crises, if they exist divorced from other phenomena, is not clear. The abdominal crises seem to be associated with changes in liver function and structure and not necessarily with increased blood destruction. The essential blood crises are the hemolytic type producing severe, even fatal, anemia. As summarized by Lowe, the clinical features of an abdominal crisis include: (1) liver enlargement; (2) repeated attacks of nausea, vomiting, fever, and progressive jaundice, with upper right quadrant pain in the presence or absence of gall stones; (3) a direct van den Bergh reaction in the serum, or one changing from indirect to direct during the acute episode. The pathologic changes observed include: (1) marked enlargement of the liver (no histologic reports, however); (2) a perilobular congestion of

characteristic type; (3) some degree of parenchymal degeneration, varying from mild with recovery to severe with terminal acute yellow atrophy.

Lowe studied carefully the pigment excretion of a 15 year old affected boy during an abdominal crisis. There was a marked sudden increase of urinary urobilin; rapid increase of bilirubinemia with change of the van den Bergh from indirect, through slight to moderate, to strong direct type; enlargement and tenderness of the liver; and diminished hippuric acid synthesis as measured by the Quick intravenous test. These findings which suggested diminished liver function then rapidly cleared with no therapeutic attempts. There was no marked increase of blood destruction associated with this series of events. In the same patient, transfusions were followed by a progressive enlargement of the spleen. There then occurred a marked increase in blood destruction, with drop of red blood cells, hemoglobin, and reticulocytes. It is probable that the transfused red cells were sequestered in the spleen and rapidly destroyed, leading to a marked stercobilin excretion. Splenectomy was followed by a return to normal in the red blood cells, hemoglobin, reticulocytes, bilirubinemia, and pigment excretion. All clinical symptoms and signs disappeared.

McLaughlin<sup>31</sup> pointed out that the manipulations of surgical removal force out into the circulation much of the blood which fills the spleen, so that this organ at the start of the operation is larger and more engorged than when finally removed and sent to the pathologist. As a consequence there ensues temporarily a striking increase in the cellular elements of the circulating blood. In counts made of his group of cases in the day following operation the average rise for hemoglobin was about 4 gm.; for red cells, 1,100,000 per c.mm.; for white cells, some 17,000 per c.mm. Thus without resorting to external transfusions an autotransfusion takes place which contributes to the success of the operation, even when a profound anemia or a hemolytic crisis is in effect. By 48 hours after operation, however, the red cell readings fall nearly to their preoperative level, due presumably to a readjustment of the fluid balance.

Sharpe and Tollman<sup>41</sup> comment that the immediate and dramatic changes in the blood picture are characteristic only of the familial variety of hemolytic anemia, for they were not observed in 5 patients (adults) who were subjected to splenectomy because of refractory atypical non-spherocytic hemolytic anemia. Freund<sup>18</sup> experienced a similar failure in an 11 year old school girl with persistent lung infection and an "acquired" chronic hemolytic anemia.

One complication which occasionally follows splenectomy consists of the building up of a tremendous platelet level within the 1st week or 2 following operation.<sup>36</sup> Diamond<sup>16</sup> described 1 such instance in a child. The high platelet count, more than 1,000,000 per c.mm. at the end of the 1st week after operation, was associated with evidences of intravascular thrombosis, manifesting itself in abdominal pain, fever, leukocytosis and convulsions. Such "platelet crises" usually subside in a relatively short time.

*Accessory Spleens.* When active symptoms begin to recur some months or years after the patient has been symptom-free following a splenectomy, one should suspect that an accessory spleen or spleens is undergoing compensatory hypertrophy. For this reason accessory spleens should be searched for and removed during the primary splenectomy. With normal adults the incidence of accessory spleens as usually stated is about 10%,

but Morrison, Lederer and Fradkin<sup>35</sup> concluded, from a study of earlier authors' work, that they are more frequent than that in childhood and still more common during the neonatal period and early infancy. Curtis and White<sup>9</sup> classified accessory spleens, according to location, as (a) hilar, (b) gonadal, and (c) gastro-intestinal. Hypertrophy of the hemolymph tissues was demonstrable at autopsy in 1 of McLaughlin's<sup>31</sup> adult cases, in which a recurrence of symptoms had occurred. Freund<sup>18</sup> had reported a 10 year old boy with congenital hemolytic anemia whose symptoms were not relieved by splenectomy; necropsy, later, uncovered a remaining accessory spleen with highly active pulp.

*Blood Changes Following Splenectomy.* It has already been stated that following splenectomy, coincident with the subsiding of the hemolysis and the anemia, the spherocytosis grows less marked, the fragility test shows an approach to more normal values though not always, the reticulocytes diminish, the platelet count is increased transitorily, and the hyperactivity of the bone marrow subsides. Howell-Jolly bodies also begin to be evident; Pepper and Austin<sup>36a</sup> found them still persistent in an adult patient 28 years after the operation, and stressed that the finding of these bodies in an otherwise normal blood can be taken as a strong indication of the absence of the spleen.

An erythroblastic response to splenectomy is, of course, well known in Mediterranean (Cooley's) anemia, also known as thalassemia. Stransky and Regala<sup>44</sup> described 2 children in a Filipino family believed to have congenital hemolytic anemia, in whom splenectomy was followed by a pronounced erythroblastic response. With both children, 3 to 5% of the red cells were erythroblasts nearly 1 year after the operation, and there were still persistent anemia, jaundice, reticulocytosis and increased urobilinogen output, indicating that the hemolytic disease had not abated. There were, however, no more hemolytic crises. Because of the failure to improve after splenectomy and since neither of these children nor their affected father displayed abnormal red cell fragility curves, one suspects that the genetic disorder of this family does not fit into the chronic hereditary hemolytic anemia under discussion here.

*Laboratory Features. Examination of the Blood.* Dameshek<sup>12a</sup> has directed attention to the information which can be gained from the ordinarily neglected but highly useful procedure of direct microscopic observation of red cells in the moist smear. In a fresh coverslip preparation of blood mixed with an anticoagulant the various degrees of spherocytosis in the individual red cells can be readily noted, since many red cells will lie edgewise to the eye. Cells in stages preliminary to complete spherocytosis will appear cup-shaped, jug-shaped, or spheroidal with a dimple at one end. Furthermore, in the presence of spherocytosis, the rouleaux formations are short, bizarre, and hardly ever straight, because it is difficult for rounded red cells to become closely aligned to others equally rounded. Gripwall<sup>21</sup> had emphasized the selfsame points; he reported also that in the fresh smear the reticulocytes are easily recognized by their distinctive "hilus" shapes. There are grooves and depressions on the surfaces of the reticulocytes which shift about slowly during time spent in their observation. These cells do not partake in rouleaux formation.

Hill<sup>24</sup> studied the dimensions of the red cells of 7 cases of congenital hemolytic anemia over a 2 year period; 3 of the patients were children. In every case but 1 there was at least 1 occasion when definite spherocytosis occurred. Decrease in diameter of the red cells—microcytosis—was also

present, except for a 7 year old boy whose red cells were often macrocytic as well as spherocytic. No significant correlation could be established between the spherocytosis and the severity of symptoms, onset of crisis, rapidity of red cell regeneration, or benefit from splenectomy.

Gripwall<sup>21</sup> described a peculiar appearance of the upper zone of the red cell layer during the performance of the Westergren sedimentation test. Above the linear upper border of the main sedimenting mass of red cells there is seen a diffuse rather homogeneous "veil-like" layer of lagging red cells. On microscopic examination this layer can be demonstrated to consist almost exclusively of hilus-shaped reticulocytes. Since they do not clump into rouleaux they settle downward more slowly than do the more mature aggregating cells. Further investigations proved that this kind of "veiled" sedimentation occurs in all conditions in which the blood contains a good proportion of reticulocytes.

*Quantitative Measurements of Fragility.* With blood from normal children the hemolysis induced by a series of increasingly hypotonic salt solutions usually begins in saline concentrations of 0.48 to 0.44% and becomes complete in concentrations 0.38 to 0.30%. One of the most characteristic diagnostic signs of congenital hemolytic anemia is a diminution in the osmotic resistance of the red cells. Disintegration becomes manifest in the zone 0.80 to 0.50% saline (normal saline = 0.85% NaCl solution) and is usually complete by 0.50 to 0.40% saline.<sup>36,38,50</sup>

Cormick<sup>7</sup> commented that the fragility test as customarily employed fails to detect slight increases in red cell fragility and should be viewed as a qualitative procedure. She recommended the more sensitive quantitative fragility method of Simmel,<sup>42</sup> which had been used by Whitby and Hynes<sup>49</sup> with adults. This method consists of hemocytometric counting of the remaining non-hemolyzed cells after exposing red cell suspensions to a series of decreasing saline solutions for 1 hour at room temperature. With 50 normal children the average values were: in 0.60% saline, 0%; in 0.55% saline, 1%; in 0.50% saline, 14%; in 0.45% saline, 47%; in 0.40% saline, 81%; in 0.35% saline, 95%. With iron-deficiency anemias and other blood dyscrasias essentially similar curves resulted. By contrast congenital hemolytic anemia (2 cases) exhibited a dramatically evident increase in red cell fragility which persisted though less marked following splenectomy.

A very similar quantitative method was utilized by Dacie<sup>106</sup> to follow more precisely the changes in fragility produced by splenectomy. In his hands the fragility curves, when classified on the basis of their shapes, fell naturally into 3 main groups—"tailed," "diagonal" and "normal." The "normal" curve rises steeply in the saline concentration zone between about 0.52 and 0.36%; the "diagonal" curves spread out in a gradual rise between 0.70 and 0.40%; the "tailed" curves overlap the "normal" for much of their course, but have traces of hemolysis in the higher concentrations of saline which form a "tail" at one end of the curve. In 11 of 12 patients on whom splenectomy was performed the red cell fragility eventually became improved, though with 7 patients having "tailed" curves the postoperative decrease in fragility was preceded by an immediately transitory increase in fragility. In 1 patient, first seen in a hemolytic crisis, the resistance to hemolysis ultimately became normal.

*Rate of Autohemolysis of Red Cells.* Dacie<sup>106</sup> investigated the question of whether the spherocytes of familial hemolytic anemia will undergo autohemolysis *in vitro* more rapidly than will normal red cells. On storing fresh blood at 37° C., whether clotted or mixed with anticoagulating potas-

sium oxalate, he found that the spherocytes of 10 patients underwent considerable spontaneous lysis within 24 hours, whereas 20 control specimens from normal individuals showed only traces at 24 hours and variable moderate amounts (trace to ++ ) after 48 hours. The rate of auto-hemolysis of the spherocytes became reduced somewhat when they were suspended in normal saline rather than serum or plasma, though disintegration under these circumstances was still more rapid than that of control washed red cells. The author suggested that the increased rate of hemolysis was perhaps dependent upon an increased *in vivo* absorption of lysolecithin by the abnormal red cells. This latter substance is a lipoidal derivative, obtainable from plasma or serum, which inhibits rouleaux formation and thereby retards sedimentation. It can convert normal discoidal red cells into spheres, with crenated and "prickle" cells as intermediate stages, and can cause hemolytic degeneration if added in sufficient concentration.

*Pathogenesis.* Ignorance still clouds our understanding of the physiologic mechanisms whose disturbed functionings result in the clinical picture of congenital hemolytic jaundice. Authorities in the field concur that one of the cardinal features of the disturbance is spherocytosis, but there is conspicuous lack of agreement as to whether the abnormally spherically red cells are that way because of a primary defect in red cell formation within the bone marrow, or because of an abnormally acting hemolytic mechanism, congenital and endogenous in origin. Dacie<sup>10b</sup> has presented an impartial appraisal of these 2 theories. The remarks and references which follow are in part extracted from his discussion.

The red cells in this condition display other abnormalities in addition to being spheroidal in shape. They can be broken up by lysolecithin more easily than normal cells.<sup>21,29,43</sup> They undergo more rapid autohemolysis *in vitro* both before and after splenectomy.<sup>10a,23,29</sup> Transfusion into healthy recipients of blood from patients with congenital hemolytic anemia has shown that the cells have a shorter life than normal,<sup>11,29</sup> whereas healthy cells have a normal survival time when transfused into patients with congenital hemolytic anemia.<sup>11</sup>

The more spheroidal shape of the cell is generally accepted as being responsible for the main features of the clinical disease, such as increased fragility to hypotonic saline, increased blood destruction, icterus, anemia, reticulocytosis, and splenomegaly. That this abnormality of the red cells, ingrained and hereditary, is the primary source of the disturbance has been proposed by many workers.<sup>21,22,29,46</sup>

In support of the opposing hemolytic agent theory is the demonstration that spherocytosis and increased fragility are not necessarily congenital in origin, but can be evoked by a variety of acquired anemias and by other diseases. Dameshek and Schwartz<sup>13</sup> energetically champion this view. From perusal of the literature and detailed hematologic study of 4 cases of acute hemolytic anemia they concluded that: (a) spherocytes are formed outside of the bone marrow; (b) spherocytosis develops only in mature red cells; (c) a hemolytic agent, such as is present in hemolytic sera, is responsible for its development.

Dacie<sup>10b</sup> lists a number of different disorders in which spherocytosis and increased fragility have been described, among them myelodysplasia and allied syndromes, leukemia, erythroblastosis fetalis, normal fetuses *in utero*, carcinomatosis of bone, lymphadenoma, ovarian dermoid cyst, lymphosarcoma of the pancreas, pneumonia, lymphadenoma, and lymphatic leukemia. The red cell changes and congestion of the spleen can

be caused also by administration of hemolytic immune sera to experimental animals<sup>13,36,47</sup> and by hemolytic poisonings in man, such as those due to sulfonamides.<sup>20,23</sup> Significantly, spherocytosis and increased fragility can be produced only *in vivo*. None of the known hemolytic agents produce these changes when added to red cells *in vitro*.

The failure to find free hemolysin in the blood of congenital hemolytic anemia cases has been explained by Dameshek and Schwartz by the hypothesis that the hemolysin responsible (of the immune body type) does not circulate in detectable amounts but remains fixed to the red cells and other tissue cells. Singer<sup>43b</sup> pointed out that this theory cannot be reconciled with the fact that normal cells, transfused into patients with congenital hemolytic anemia, have a normal longevity.<sup>11</sup>

Josephs<sup>25</sup> suggested that in congenital hemolytic jaundice some substance may be lacking which in normals helps to maintain the normal equilibrium between formation and destruction of blood.

The persistence of abnormal cells after removal of the spleen demonstrates that this organ alone is not responsible for the abnormalities, though its removal reduces the rate of hemolysis to limits which can be satisfactorily compensated for.

The mechanism of hemolysis within the spleen is not clear. Erythrophagocytosis is generally inconspicuous, indicating a humoral rather than a cellular type of destruction. Some authors<sup>17,21</sup> have attributed hemolysis to the action of lysolecithin<sup>3,4</sup> produced in excessive quantities by a spleen in which an unusual degree of circulatory stasis is assumed to occur. Recent claims<sup>21,29,43a</sup> that the red cells in familial hemolytic anemia are unusually sensitive to the hemolytic effect of lysolecithin appear to fit in with these ideas. Ham and Castle<sup>23</sup> believe that circulatory stasis of a normal degree, acting upon cells which are unusually susceptible to its effects, is sufficient to account for the increased hemolysis. Whipple<sup>48</sup> and Dacie<sup>10b</sup> suggest that stagnation in the spleen may be selective; normal discoidal cells may have no difficulty in traversing the spleen, but spherocytes, possibly because of their spheroidal shape, cannot pass through the stomata of the splenic sinuses.

#### REFERENCES

- (1.) Abt, A. F.: *Am. J. Dis. Child.*, 60, 812, 1940.
- (2.) Bell, L. P.: *Surg., Gynec. and Obst.*, 50, 606, 1930. (3.) Bergenhem, B.: *Acta path. Microbiol. Scand.*, Suppl. 39, 1939. (4.) Bergenhem, B., and Fahraeus, R.: *Ztschr. f. d. ges. exp. Med.*, 97, 555, 1936. (5.) Blackfan, K. D., Diamond, L. K., and Leister, C. M.: *Atlas of the Blood in Children*, New York, Commonwealth Fund, 1944.
- (6.) Cooper, E. L.: *Ann. Int. Med.*, 15, 858, 1941. (7.) Cormick, J.: *Arch. Dis. Child.*, 17, 227, 1942. (8.) Curtis, G. M., Doan, C. A., and Wiseman, B. K.: *Ann. Surg.*, 104, 892, 1936. (9.) Curtis, G. M., and White, P. L.: *Trans. West. Surg. Assn.*, 46, 364, 1937.
- (10.) Dacie, J. V.: (a) *J. Path. and Bact.*, 52, 331, 1941; (b) *Quart. J. Med.*, n.s., 12, 101, 1943. (11.) Dacie, J. V., and Mollison, P. L.: *Lancet*, 1, 550, 1943. (12.) Dameshek, W.: (a) *New England J. Med.*, 221, 1009, 1939; (b) *Ibid.*, 224, 52, 1941. (13.) Dameshek, W., and Schwartz, S. O.: *Am. J. Med. Sci.*, 196, 769, 1938. (14.) Debré, R., Lamy, M., Sée, G., and Schrameck, G.: *Am. J. Dis. Child.*, 56, 1189, 1938. (15.) Dedichek, H. G.: *Norsk. mag. f. Lægevidensk.*, 98, 279, 1937. (16.) Diamond, L. K.: *Med. Clin. North America*, 21, 401, 1937.
- (17.) Fahraeus, R.: *Lancet*, 2, 630, 1939. (18.) Freund, M.: *Am. J. Dis. Child.*, 43, 645, 1932.
- (19.) Gairdner, D.: *Arch. Dis. Child.*, 14, 109, 1939. (20.) Gilligan, D. R., and Kapnick, I.: *New England J. Med.*, 224, 801, 1941. (21.) Gripwall, E.: *Acta med. Scandinav.*, Suppl. 96, 1938.
- (22.) Haden, R. L.: (a) *Am. J. Med. Sci.*, 188, 441, 1934; (b) *J. Lab. and Clin. Med.*, 26, 65, 1940; (c) *Surg. Clin. North America*, 21, 1453, 1941; (d) *Proc. Interst. Post-*

grad. Med. Assn. North America (1942), vol. 112, 1943. (23.) Ham, T. H., and Castle, W. B.: *Proc. Am. Phil. Soc.*, 82, 411, 1940. (24.) Hill, J. M.: *J. Am. Med. Assn.*, 111, 2179, 1938.

(25.) Josephs, H. W.: *Bull. Johns Hopkins Hosp.*, 62, 25, 53, 1938.

(26.) Klemperer, P.: *Handbook of Hematology*, edited by Hal Downey, New York, Hoeber, 1938.

(27.) Lawrence, J. S.: *Internat. Clin.*, 2, 221, 1937. (28.) Lippman, E. S.: *Journal-Lancet*, 62, 188, 1942. (29.) Lloyd, T. W.: *On the Aetiology of Acholuric Family Jaundice*, Oxford Univ. Thesis, 1941 (cited by Dameshek<sup>13b</sup> and Dacie<sup>14b</sup>). (30.) Lowe, R. C.: *Am. J. Med. Sci.*, 206, 347, 1943.

(31.) McLaughlin, C. W.: *Surgery*, 12, 419, 1942. (32.) McLaughlin, C. W., Sharpe, J. C., and Cunningham, R.: *New Internat. Clin.*, 4, 108, 1941. (33.) McNee, J. W.: *Lancet*, 1, 1063, 1931. (34.) Meulengracht, E.: *Deutsch. Arch. f. klin. Med.*, 136, 33, 1921. (35.) Morrison, M., Lederer, M., and Fradkin, W. Z.: *Am. J. Med. Sci.*, 176, 672, 1928.

(36.) Pearce, R. M., Krumbhaar, E. B., and Frazier, C. H.: *The Spleen and Anemia*, Philadelphia, Lippincott, 1918. (36a.) Pepper, O. H. P., and Austin, J. H.: *J. Am. Med. Assn.*, 122, 870, 1943.

(37.) Race, R. R.: *Ann. Eugenics*, 11, 365, 1942. (38.) Rohr, K.: *Helvet. med. Acta*, 10, 31, 1943.

(39.) Scott, A. M.: *Lancet*, 2, 872, 1935. (40.) Sharpe, J. C., and Davis, H. H.: *J. Am. Med. Assn.*, 110, 2053, 1938. (41.) Sharpe, J. C., and Tollman, J. P.: *Arch. Int. Med.*, 70, 11, 1942. (42.) Simmel, H.: *Deutsch. Arch. f. klin. Med.*, 142, 252, 1923. (43.) Singer, K.: (a) *Am. J. Med. Sci.*, 199, 466, 1940; (b) *J. Lab. and Clin. Med.*, 30, 784, 1945. (44.) Stransky, E., and Regala, A. C.: *Am. J. Dis. Child.*, 63, 859, 1942.

(45.) Teall, C. G.: *Brit. J. Radiol.*, 12, 601, 1939. (46.) Thompson, W. P.: *Bull. Johns Hopkins Hosp.*, 51, 365, 1932. (47.) Tigertt, W. D., and Duncan, C. N.: *Am. J. Med. Sci.*, 200, 173, 1940.

(48.) Whipple, A. O.: *Trans. and Stud. Coll. Phys. Phila.*, 8, 203, 1941. (49.) Whitby, L. E. H., and Hynes, M.: *J. Path. and Bact.*, 40, 219, 1935. (50.) Wiedemann, H. R.: *Ztschr. f. Kinderheilk.*, 63, 501, 1942.

## PHYSIOLOGY

### PROCEEDINGS OF

### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 16, 1945

**An Evaluation of the Effectiveness of Globin, Albumin, Hemoglobin and Oxypolygelatin in the Treatment of Hemorrhagic Shock.\*** A. S. HAMILTON and W. M. PARKINS (Harrison Dept. of Surgical Research, Univ. of Penna.) The efficacy of colloid solutions as plasma substitutes following hemorrhage has been tested by two procedures. These procedures were planned to produce moderate and severe degrees of circulatory deficiencies.

Thirty-five dogs under light nembutal anesthesia were bled (4 cc. per kg. per minute) to a blood pressure end-point of 20 mm. Hg and immediately infused with a volume of fluid equal to the blood volume removed. A second hemorrhage, 3 hours post-infusion, was performed at the same rate and to the same end-point as the initial hemorrhage and was followed by the infusion of erythrocytes in the replacement fluid.

The following factors were considered in evaluating the efficacy of infusion fluids: degree and variation in hemodilution, change in plasma density, restoration and maintenance of blood pressure, volume of second bleeding, and survival.

The average volume of the second hemorrhage expressed as percentage

\* Work done under contract with the Office of Scientific Research and Development.

of the initial bleeding volume was as follows: saline, 48; 3.3% human globin, 43; plasma, 65; 7% hemoglobin, 73; 5% oxypolygelatin, 79; 5% albumin, 88; and autotransfused blood, 95. Rapid infusion of modified human or dog globin produced vasomotor disturbances in normal dogs and was not well tolerated by severely bled dogs.

Immediately preceding the second bleeding the average hematocrit values expressed as percentage of the control value were as follows: oxypolygelatin, 33; hemoglobin, 39; 5% albumin, 41; plasma, 44; globin, 55; and saline, 66. Hemoconcentration was evident in hemoglobin-infused animals 24 hours after hemorrhage.

Blood pressure approached normal values, and was well maintained with each of the replacement fluids. The best restoration of blood pressure was obtained with autotransfused blood.

In 22 experiments, 1 hour of hypotension at 30 mm. Hg preceded the infusion. According to the criteria used in these more severe hemorrhage shock experiments plasma consistently gave the most favorable results. Albumin (5 and 25%) and oxypolygelatin were definitely superior to saline. The concentrated albumin required about  $1\frac{1}{2}$  to 3 hours to produce a degree of dilution comparable to that obtained with plasma.

**The Effects of Alterations in the Arterial Tensions of Carbon Dioxide and Oxygen on the Cerebral Blood Flow and Cerebral Oxygen Consumption of Normal Young Men.\*** S. S. KETY and C. F. SCHMIDT (Dept. of Pharmacology, Univ. of Penna.) By means of the nitrous oxide method previously reported,<sup>1</sup> quantitative measurements were made of blood flow and oxygen consumption in the brains of unanesthetized healthy young men under normal basal conditions and during active and passive hyperventilation with room air, inhalation of 5 and 7% CO<sub>2</sub> with 21% O<sub>2</sub>, of 85 to 100% O<sub>2</sub>, and of 10% O<sub>2</sub>. The average results are presented in Table 1:

TABLE 1.—CHANGES IN CEREBRAL BLOOD FLOW AND OXYGEN CONSUMPTION UNDER THE VARIOUS CONDITIONS

Experimental procedure	No. subjects	Cerebral blood flow (cc./100 gm./min.)			Cerebral O <sub>2</sub> consumption (cc./100 gm./min.)		
		Control	Exp.	Change (%)	Control	Exp.	Change (%)
1. Active hyperventilation	7	70	47	-32	4.3	4.9	+15
2. Passive hyperventilation	5	66	41	-36	4.7	4.7	0
3. 5% CO <sub>2</sub> inhalation . .	6	71	112	+58	4.2	4.6	+9
4. 7% CO <sub>2</sub> inhalation . .	2	64	144	+125	4.0	3.7	-8
5. 85-100% O <sub>2</sub> inhalation.	6	67	59	-12	4.1	4.1	0
6. 10% O <sub>2</sub> inhalation . .	3	75	111	+48	4.2	4.1	-2

The changes in cerebral blood flow induced by both types of hyperventilation, by 5% CO<sub>2</sub> and by high oxygen are all statistically significant. The results reported for low oxygen are not yet significant, due to the small number of cases, but these experiments are being continued. The reported changes in cerebral oxygen consumption are not statistically significant, except for the increase associated with active hyperventilation which was a constant finding in all experiments in that group.

It is pointed out that similar conclusions concerning changes in cerebral blood flow in man during these procedures were reached previously by others<sup>2</sup> using the cerebral arteriovenous oxygen difference as a measure of

\* Work done under contract with the Office of Scientific Research and Development.



cerebral blood flow with the unestablished assumption that cerebral oxygen consumption remained constant. Although the present data validate this assumption under these specific conditions, there is still no warranty that under other conditions the cerebral oxygen consumption would remain constant. Recently it was found<sup>3</sup> that under a wider range of conditions cerebral arteriovenous oxygen difference was a very poor criterion of cerebral blood flow. This would be expected since the arteriovenous oxygen difference, being a product of both blood flow and oxygen consumption, is alone a measure of neither.

From our control data it is now possible to derive a first approximation to the total cerebral blood flow and oxygen consumption of the human brain under basal conditions and the respective proportion of those to cardiac output and total oxygen consumption. These data on the basis of a brain weight of 1400 gm. are presented in Table 2. We are continuing this work with further studies on the physiology, pharmacology and pathology of the cerebral circulation in man.

TABLE 2.—CEREBRAL BLOOD FLOW AND OXYGEN CONSUMPTION IN RELATION TO CARDIAC OUTPUT AND TOTAL OXYGEN INTAKE

Subject	Cerebral blood flow		Cerebral oxygen consumption	
	Cc./min.	% of cardiac output*	Cc./min.	% of total O <sub>2</sub> intake by body
SH . . . .	826	20.2	55	20.1
LE . . . .	925	18.2	64	24.0
MH . . . .	896	20.4	60	21.6
OM . . . .	1050	21.4	69	29.8
WH . . . .	938	20.0	62	24.4
Mean . . . .	927	20.0	62	24.0

\* Cardiac output calculated from ballistocardiograms using the original formula of Starr *et al.*<sup>4</sup> and the correction factor 1.18 of Cournand *et al.*<sup>5</sup>

#### REFERENCES

1. KETY, S. S., and SCHMIDT, C. F.: *Am. J. Physiol.*, 143, 53, 1945.
2. LENNOX, W. G., and GIBBS, E. L.: *J. Clin. Invest.*, 11, 1153, 1932.
3. SCHMIDT, C. F., KETY, S. S., and PENNES, H. H.: *Am. J. Physiol.*, 143, 33, 1945.
4. STARR, I., RAWSON, A. J., SCHROEDER, H. A., and JOSEPH, N. R.: *Am. J. Physiol.*, 127, 1, 1939.
5. COURNAND, A., RANGES, H. A., and RILEY, R. L.: *J. Clin. Invest.*, 21, 287, 1942.

**Respiratory Flow Rates and the Design of Oxygen Equipment.\*** J. R. PAPPENHEIMER, J. C. LILLY and G. A. MILLIKAN (Johnson Research Foundation, Univ. of Penna.). A knowledge of respiratory flow rate patterns under various conditions of physical activity and resistance to breathing is of basic importance in determining specifications for the manufacture of oxygen delivery systems, respiratory filters, valves and other respiratory equipment. Records were shown illustrating typical respiratory flow patterns and static and dynamic pressure-flow characteristics of certain respiratory equipment. The importance of such measurements for ensuring an adequate oxygen supply and a tolerable resistance to breathing in aviation, industrial and clinical applications was pointed out.

**The Effect of Morphine Upon the Circulatory and Respiratory Responses to Tilting.** J. H. DREW, R. D. DRIPPS, JR., and J. H. COMROE, JR. (Depts. of Neurosurgery and Anesthesia, Hosp. of the Univ. of Penna., Harrison

\* Work done under contract with the Office of Scientific Research and Development.

Dept. of Surgical Research and the Dept. of Pharmacology, Univ. of Penna. School of Medicine). It is generally thought that morphine produces no significant change in the circulation in man. However, individuals given morphine often develop symptoms such as faintness, giddiness, or dizziness which are suggestive of some alteration in the circulation. Since these symptoms occur more frequently in the upright position, we decided to investigate the effects of morphine upon the circulation of supine and erect man. Morphine was injected intravenously in 25 supine subjects; while blood pressure did not change significantly, pulse increased an average of 27 % and cardiac output per minute, as measured by the ballistocardiograph, increased 23 %. These results indicated that morphine does alter the circulation in supine man but that compensatory mechanisms prevent any detectable change in blood pressure. The circulation was then put under a strain by tilting subjects from the horizontal to 75° feet down position for 10 to 15 minutes. Before morphine only 2 of 25 subjects (8%) fainted while after administration of morphine intramuscularly 11 of 25 (44%) fainted. When the legs and thighs of these 11 were wrapped tightly with elastic bandages, only 2 of 11 (18%) fainted upon retilting. The actual site of action of morphine upon the circulation cannot be stated definitely from these data but we believe that the effect is predominantly due to peripheral vasodilatation for the following reasons: (1) Morphine did not decrease the cardiac output and hence the fall in blood pressure could not be due to direct cardiac depression. (2) It did not depress the immediate increase in pulse rate that normally occurs upon tilting, and therefore the pressure receptors and cardio-accelerator centers were not depressed by morphine. (3) The decrease in respiration was not sufficient to decrease venous return significantly.

Certain clinical implications may be derived from these experiments. Morphine should not be used unless necessary in patients who are in the erect or sitting position, or in patients whose circulation is under other strain, such as hemorrhage or shock, unless precautions are taken to prevent pooling of blood in the extremities.

Observations were also made upon the respiratory responses to tilting. Upon tilting to the feet down position, respiratory minute volume decreased 10%, whereas upon tilting back to the horizontal, minute volume increased 28%. The unexpectedly greater change upon returning the patient back to the horizontal position was probably due to distention of pulmonary capillaries by blood previously pooled in the legs.

Respiration and circulation were measured at the moment of syncope in 11 subjects. The remarkable finding was the small respiratory increase (20%) that occurred. This together with a frequent finding of pulse slowing indicates that the usual peripheral pressure-receptor and central vasomotor regulatory mechanisms either fail to respond or are suppressed under these circumstances in unanesthetized man.

# BOOK REVIEWS AND NOTICES

---

**TEXTBOOK OF OBSTETRICS.** By HENRICUS J. STANDER, M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Cornell University Medical College; Obstetrician and Gynecologist-in-Chief, New York Hospital and Director of the Lying-in Hospital, New York City. Third Ed. (representing the Ninth Ed. of Williams Obstetrics, the first six of which were written by the late Dr. J. Whitridge Williams). Pp. 1277; 740 figs. New York: D. Appleton-Century, 1945. Price, \$10.00.

THIS new edition contains a few less pages and illustrations than the previous edition. It has been improved by the withdrawal of certain illustrations which gave what might be described as an old fashioned atmosphere, and by the introduction of many line drawings which represent the best type of pictures for many subjects, especially the mechanism of labor.

The discussions of the various subjects are well presented and well documented. Although briefer texts may be preferred by beginning students, the reviewer is convinced that the more comprehensive texts such as the present one have greater general and ultimate value. They supply a broader background of ideas as well as facts. The present edition perpetuates the high standard of medical writing set by Williams in the first 6 editions, and is not excelled in the field of obstetrical texts printed in English. D. M.

---

**TEXTBOOK OF BACTERIOLOGY.** By EDWIN O. JORDAN, PH.D., late Professor of Bacteriology and WILLIAM BURROWS, PH.D., Associate Professor of Bacteriology, University of Chicago. Fourteenth Ed. Pp. 909; 242 ills. Philadelphia and London: Saunders, 1945. Price, \$7.00.

As an extremely well-rounded source of bacteriological information, this textbook should be welcome to medical students and medical technicians principally. It makes no attempt to fill the needs of students of other branches of bacteriology. The presentation follows an orderly and logical plan. The early chapters deal with the history of bacteriology, general considerations of microorganisms, the relation of bacteria to disease in humans, followed by host-parasite relationships. The bacteriology of environment with specific discussions of water, sewage, milk, and food examinations and treatment precede chapters on antigen-antibody reactions, immunology, and allergy. Then the remaining chapters consider the pathogenic bacteria, fungi, rickettsia, and viruses. Human parasitology is given a fairly extensive treatment for a book of this size in addition.

Particular attention is drawn to biological interrelations found in the study of the various types of microorganisms. Individually the microorganisms are considered not only from their biologic characteristics, but also their accepted diagnostic procedures, their immunochemical attributes, their epidemiological considerations, the disease forms produced in man, the type of immunological response, and biological prophylaxis and treatment follow. In addition related, non-pathogenic members are considered briefly.

The chapter on fungi is well illustrated with numerous photomicrographs of the various pathogenic species to supplement the text which covers the field remarkably well. The section on antigen-antibody reactions presents the modern theories for the mechanism of precipitation in a clear, concise manner. The discussion of allergy, however, is too brief for medical students and considers only the classical concepts of hypersensitivity, avoiding the recent work on abnormal types of antibodies such as the work of Loveless on reagin. Antibiotics and sulfonamides are considered sufficiently, but only in relation to bacterial physiology and to the mechanism of chemical bacteriostasis. The

term "semi-solid media" is defined in the early sections as referring to media containing 1.5% agar and it is used in this sense throughout the book. Such usage may be confusing to the student who also learns to speak of media containing 0.5% agar as "semi-solid."

The illustrations and charts used in this book are modern and pertinent. The author has made good use of electron micrographs in instances where the increased magnification permits visualization of otherwise invisible structures. References are given as footnotes and at times seem scanty in supporting statements made in the text. In general where controversial subjects are considered, the author usually takes a definite stand and expresses an opinion. Long, tedious, often uncritical, pro and con discussions of such subjects are thus eliminated.

On the whole this textbook of bacteriology is well suited to the needs of students in the medical and public health fields and for such needs it is heartily recommended. J. F.

---

A TEXT-BOOK OF PHARMACOGNOSY. By GEORGE EDWARD TREASE, Lecturer on Pharmacognosy and Acting Head of the School of Pharmacy in the University College of Nottingham, England. Pp. 782; 280 figs. Fourth Ed. Baltimore: Williams & Wilkins, 1945. Price, \$7.50.

THIS book doubtless is useful for the purpose stated in the introduction, viz., to cover the requirements in pharmacognosy for pharmaceutical examinations in most English-speaking countries; but it would be more valuable in this country if it dealt even to a small extent with substances listed in the U.S.P. and N.F. The only U.S.P. drug mentioned is Eriodictyon; even so characteristically American a drug as Cascara carries no statement of the U.S.P. name or characteristics. Most of the substances described are obsolete as drugs, though some have importance in industry. The book would have small attraction for physicians of any country and would be inferior to American texts on pharmacognosy for its avowed purpose in the U. S. C. S.

---

SCIENCE IN PROGRESS. By WALTER R. MILES, and others. Foreword by LORANDE LOSS WOODRUFF. Edited by GEORGE A. BAITSELL. Fourth Series. The Society of the Sigma Xi, National Lectureships 1943 and 1944. Pp. 331; 106 ills. New Haven: Yale Univ. Press, 1945. Price, \$3.00.

THIS is the fourth published collection of the inspiring Sigma Xi lectures. The roster of contributors comprises 11 distinguished workers in a variety of branches of scientific research. Of special pertinence to physicians are the discussion of psychologic aspects of military aviation, by Walter R. Miles; physical structure and biologic action of nerve cells, by Detlev W. Bronk; energy and vision, by Selig Hecht; chemical transmission of nerve impulses, by Otto Loewi; present status of the Vitamin B complex, by C. A. Elvehjem; and blood and blood derivatives, by Edwin J. Cohn. The remaining chapters, by George D. Birkhoff, Peter Debye, Henry Eyring, Isadore I. Rabi, and K. C. D. Hickman, describe subjects less closely related to medicine, yet of significance to us by furnishing a background of cultural information. I. W.

---

A PRIMER OF ELECTROCARDIOGRAPHY. By GEORGE BURCH, M.D., F.A.C.P., Associate Professor of Medicine, Tulane University School of Medicine, etc., and TRAVIS WINSOR, M.D., Instructor in Medicine, Tulane University School of Medicine, etc. Pp. 215, 235 ills. Phila.: Lea & Febiger, 1945. Price, \$3.50.

STUDENTS of electrocardiography appear to be dividing themselves into two schools of thought so far as the fundamentals of that subject are concerned. One school, numerically far the larger at this time utilizes the Einthoven equilateral triangle hypothesis and the assumptions which underlie it as the base upon which their superstructure is erected, largely with the aid of mathematical reasoning. The other school, which does not accept certain

of Einthoven's assumptions on the ground that available evidence does not support them, is interested in attempts to demonstrate relationships between potential variations of cardiac and body surface areas by purely experimental methods. The first school has a ready explanation for almost any conceivable deflection that may be encountered in an electrocardiogram while the second is having considerable difficulty in getting its science out of the swaddling clothes stage.

This book, which is intended to acquaint the beginner in electrocardiography with the fundamentals of the subject, adheres to the doctrines of the Einthoven school and does not mention other views. The text is clearly written and the illustrations superb. The book will doubtless prove completely satisfactory to those who accept the assumptions upon which it is based. This reviewer would like to point out, however, that Einthoven's law to the effect that the algebraic sum of the deflections in Leads I and III at any instant equals that of Lead II is not proven by Kirchhoff's law about currents in a network but is the expression of a simple identity that would have to hold for the relationships among any 3 positions on any body.

C. W.

---

**CLINICAL PARASITOLOGY.** By CHARLES FRANKLIN CRAIG, M.D., M.A. (Hon.), F.A.C.S., F.A.C.P., Col. U. S. A. (Retired), D.S.M., Formerly Director, Army Medical School, Washington, D. C.; Emeritus Professor of Tropical Medicine in Tulane University, and ERNEST CARROLL FAUST, M.A., Ph.D., Professor of Parasitology in the Department of Tropical Medicine, Tulane University; Consultant to the Secretary of War, Army Epidemiologic Board on Epidemic and Tropical Diseases; Consultant U. S. Public Health Service; Honorary Consultant, Army Medical Library. Fourth Ed. Pp. 871; 305 engravings and 4 colored plates. Phila.: Lea & Febiger, 1945. Price, \$10.00.

THIS revised edition of what is universally recognized as an authoritative standard text will be welcomed by all who try to keep abreast of progress in Parasitology. The first section is a General Introduction, which contains, among other orienting material, an excellent Digest of the International Rules of Zoological Nomenclature. (This chapter makes the book of especial service to those interested in zoology and taxonomy.) There follow 4 exhaustive sections entitled "Protozoa and Protozoan Infections," "Helminth and Helminthic Infections," and "Arthropods and Human Disease." Technical procedures and references to the literature complete the presentation. Illustrative photographs and line drawings are abundant, and there are some excellent color plates on malaria recognition. As a feature of this new edition, lucid paragraphs on pathogenesis have been added to each description of disease. Such discussions of the pathologic physiology of the disturbances add greatly to one's understanding of the how and why, and thereby contribute to the usefulness of this book as a text for medical students.

I. W.

---

**A MANUAL OF THE ASPERGILLI.** By CHARLES THOM, Collaborator, Northern Regional Research Laboratory, formerly Principal Mycologist, Bureau of Plant Industry, U. S. Dept. of Agriculture, Washington, D. C., and KENNETH B. RAPER, Senior Microbiologist, Fermentation Division, Northern Regional Research Laboratory, Bureau of Agricultural and Industrial Chemistry, U. S. Dept. of Agriculture, Peoria, Ill. Pp. 373; 76 figs. Baltimore: Williams & Wilkins, 1945. Price, \$7.00.

To biologists, the name of Thom has been almost synonymous with *Aspergilli* for many years; up to the present, his book on *Aspergilli*, written in 1926 in collaboration with Church, has been the main source of information on the subject. In this second book, Science has been fortunate in his association with Raper, who added his knowledge of chemistry and of microbiology in general to Thom's store of other information and experience.

The *Aspergilli* have been covered exhaustively. Part I is devoted to generalities, covering classification, morphology, methods of laboratory examination and the most important subject of variation. Part II comprises the bulk of

the book because here the characteristics of the various aspergillotic groups, species and forms are described. Thousands of strains of *Aspergilli* in culture. Under each group of the *Aspergilli*, there appear parts devoted to morphology, chemistry and perhaps pathogenesis. Part III is particularly appreciated by physicians because, in addition to a check list of species, it supplies bibliographies, arranged both according to author and by topics. In these days when antibiotics have focussed attention on the chemistry of fungi, this topical bibliography will have special appeal; the following subjects furnish headings: The production of acids (citric, fumaric, gallic, gluconic, itatonic, kojic, oxalic), antibiotics and toxins, chemistry of mold tissue, enzyme production, fat production, pathogenicity, physiology, pigments, vitamins, alcohol, ergosterol, fluorescein, hydroxylamine, and others. This topical bibliography covers three pages.

The book does not contain a separate chapter on pathogenicity or fungous disease, such as many physicians would desire. This is understandable because, as the authors state, as a manual of the *Aspergilli* it need not exhaustively cover the diseases they produce. Their story is of the *Aspergilli*. The authors, not being physicians, direct their attention toward the fungus rather than the fungous disease. None the less, data on pathogenesis are supplied in a limited way in connection with the description of those *Aspergillus* groups which have any pathogenic features, *e. g.*, in the discussion of *A. fumigatus*. The section on pathogenesis in the topical index supplies an extensive bibliography.

The straightforward text makes easy reading. The pages abound with illustrations of high quality. This reviewer finds such difficulty in entering an item on the debit side of the ledger that he is forced to resort to extremes by citing the color illustrations. In some of them, the green color is overdone, but this is seldom serious enough to interfere with the message intended. The authors will be rewarded for their knowledge, skill and labor because the book will be the last word on the *Aspergilli* for many years to come. F. W.

---

**A HANDBOOK FOR DISSECTORS.** By J. C. BOILEAU GRANT, M.C., M.B., CH.B., F.R.C.S. (EDIN.), Professor of Anatomy, University of Toronto, and H. A. CATES, M.B., Associate Professor of Anatomy, University of Toronto, Toronto, Canada. Second Ed. Pp. 390; 10 figs. Baltimore: Williams & Wilkins, 1945. Price, \$2.50.

THIS dissecting guide was originally written to be used with the senior author's text-book, "A Method of Anatomy." Now the authors deem it "desirable to let the handbook exist in its own right." Consequently, some extensive changes have been effected. Former page references to "A Method of Anatomy" have been deleted and instructions for the dissection of particular parts included. All chapters, except the one on the brain, now begin with some explanatory or descriptive matter furnishing further information about the region to be dissected. A general introductory chapter and index have been added. The text proper has been increased by some 125 pages. The figures, as in the earlier edition, show the various skin incisions to be made.

The book is an admirable, concise and thoroughly systematic *vade-mecum* for the medical student in his first exploration of the human body. It is intended, not to substitute for the larger, descriptive texts, but to promote an intelligent approach to the methodology of dissection. Although very different in many obvious respects from Cunningham's 3 volume *Manual*, the *Handbook* should serve as a really practicable alternative to the almost intolerable length of the *Manual*. From a practical standpoint, the only drawback—one inherent in all dissecting guides—is that once a specific book of this sort is adopted it can seldom be adapted. It must be used in its entirety or not at all. The present work errs in this respect less than most.

This well planned little volume, then, should fill a definite need for those seeking a complete laboratory dissecting guide.

J. P.

**GOVERNMENT IN PUBLIC HEALTH.** By HARRY S. MUSTARD, M.D., LL.D., DeLamar Professor of Public Health Practice, Columbia University. Pp. 219. New York: The Commonwealth Fund, 1945. Price, \$1.50.

THIS volume is the second study to be published under the auspices of the New York Academy of Medicine Committee on Medicine and the Changing Order. It is an excellent book. The author has fulfilled admirably the request of the Committee by giving not only a clear picture of government-supported public health organization and operation, as it now exists in this country, but also political and social evolution as related to public health and "perspectives to help chart the direction of future developments."

The book first lays the groundwork for an understanding of public health. Both the biological and the sociological factors in health and disease are discussed, the character of public health problems, the professions that participate in public health work and their education and the relation of government to public health work are briefly and wisely considered. As the author expresses his conviction that it is around the practicing physician, representing medical science, that public health programs must be built, it is clear that his book has been written for the rank and file of the medical profession.

A large part of the chapter on Federal Health Services is devoted to the fascinating story of the evolution of public health, beginning with its inception in a report on Marine Hospitals by Alexander Hamilton in 1792. The present somewhat confused status of Federal Public Health is considered, and its weakness as well as its strength and value set forth.

State and local health departments are discussed, and the handicaps under which they work in our present form of political and social organization are described. The problem of integrating public health work as conducted in the three "areas of Government," Federal, State and local, is clearly presented and analyzed.

After a discussion of the various activities of Government in a public health program, an excellent summary of trends and a consideration of certain needs concludes the book.

This small and well written volume should be widely read by public spirited people both within and without the medical profession as it gives a clear understanding of the struggles going on in this country to preserve and improve the health of all our citizens. The present shortcomings and urgent needs are emphasized and it is the sort of book that every medical student should be encouraged to read if we are to aim in our medical schools to turn out scholars and citizens to take their proper place in our present day society. G. R.

---

**CLINICAL CASE TAKING.** Guides for the Study of Patients. History Taking and Physical Examination or Semiology of Disease in the Various Systems. By GEORGE R. HERRMANN, M.D., Ph.D., Professor of Medicine, University of Texas. Third Ed. Pp. 192. St. Louis: C. V. Mosby, 1945. Price, \$1.75.

THIS is a small compact book of considerable interest. An introduction touches briefly on the philosophy of clinical medicine, the objectives, the principles and practise, the art and technique of case-taking. A section descriptive of various divisions of a case record is followed by detailed routine outlines for history taking and for physical examination. There is considerable emphasis on the patient's mental make-up. The "Family History" is perhaps too detailed, and to the reviewer the outline for physical examination seems less well-balanced than the other sections. There is much emphasis on habitus and constitution, whereas outlines of examination for lungs, heart and abdomen are brief and incomplete. Another criticism relates to listing as "routine" such special studies as instrumental examination of the rectum and examination of sputum, gastric contents and feces. Minor criticisms relate to lack of careful proof-reading, with frequent omission of punctuation and failure to indicate clearly distinctions between headings and subheadings.

Well over half the book is devoted to case-taking in special groups of diseases: allergic, nutritional, lung, heart, peripheral vascular, etc. Effort is

made to record in some completeness all questions and examinations required in these groups. An enormous number of signs, symptoms and tests are mentioned, and the reader's medical vocabulary is increased. In some groups of cases, however, the method used is not entirely successful. Endocrine and metabolic diseases may have much in common, but the addition of hematologic disorders to the group only makes for confusion. It takes considerable mental agility to sort out the symptoms mentioned in dealing with a particular patient. For students and less experienced physicians for whom this book is primarily designed, a simpler approach would be preferable.

The form of the book is excellent, as is the use of bold faced type for painting up examinations that form the indispensable framework in every record. However, above all, the experiences and attitudes of the author as expressed in the early pages of this little volume are profoundly worthy of emulation and cannot but be helpful to younger doctors as they develop their own physician-patient relationships.

J. M.

---

THE PHOTOCHEMISTRY OF GASES. By WILLIAM ALBERT NOYES, JR., Professor of Chemistry, Univ. of Rochester, and PHILIP ALBERT LEIGHTON, Professor of Chemistry, Stanford Univ. American Chemical Society Monograph Series, No. 86. Pp. 475. New York: Reinhold Publishing Corp., 1941. Price, \$10.00.

PHOTOCHEMISTRY is a highly specialized field, which is of growing interest from the biologic viewpoint. One need merely mention such applications as photochemical processes associated with chlorophyll, sensitization phenomena related to porphyrins, the production of vitamin D by ultraviolet irradiation of ergosterol, the functional chemistry of visual purple, and the destruction of proteins and enzymes by ultraviolet light.

Earlier volumes in this monographic series have been devoted more exclusively to the applied phases of photochemistry: "Photochemical Processes," No. 43, by G. Kistiakowsky, "Photodynamic Action and Diseases Caused by Light," No. 85, by H. E. Blum, and "The Chemical Action of Ultraviolet Rays," by C. Ellis and A. A. Wells. The present monograph by Professors W. A. Noyes and P. A. Leighton is an authoritative, though technical, exposition of the fundamental theories of photochemistry and its related subject, spectroscopy. A particularly valuable feature of the book are the appendices which list all known photochemical reactions, both simple and complex substances being included. The monograph is highly recommended to all interested in the study of photochemistry.

D. D.

---

FACIAL AND BODY PROSTHESES. By CARL DANE CLARK, PH.D., Associate Professor of Art as Applied to Medicine, School of Medicine, Univ. of Maryland; Captain, Sanitary Corps, Army of the United States, Department of Moulage and Prosthetics, Army Medical Museum. Pp. 200; 75 ills. St. Louis: C. V. Mosby, 1945. Price, \$5.00.

THE replacement by artificial substances of tissues lost by injury or disease is of particular interest and concern during the present period of post-war reconstruction. While surgical replacement is desirable whenever possible, artificial restoration by moulage has a definite place: (1) as a temporary substitute during the course of surgical reconstruction, and (2) in cases where the mutilation is too extensive or the age of the patient or conditions of health preclude surgery. The author has brought up to date and describes in detail the materials and technique employed in replacing defects of the cranium, nose, ear, cheek, hand, etc., by artificial means. One omission noted is the making of artificial eyes of acrylic resin, the development of which is one of the outstanding contributions of the Army and Navy Dental Corps during the recent war. It is hoped that in a future edition this subject will be included.

Dr. Clark has provided a useful guide to those who wish to apply their artistic talents to this particular field.

R. I.



**CENTRAL AUTONOMIC REGULATIONS IN HEALTH AND DISEASE, WITH SPECIAL REFERENCE TO THE HYPOTHALAMUS.** By HEYMEN R. MILLER. Pp. 430; 61 ill. New York: Grune & Stratton, 1942. Price, \$5.50.

THE central integration of the relatively well established peripheral autonomic mechanisms is reviewed. It should be realized that the rôle of the hypothalamus and hypothalamo-cortical integration pathways is a most complex and controversial subject. Nevertheless, such an attempt to summarize the experimental evidence under the headings of clinically important bodily functions is worth the attention of all practising physicians. Clinical material is presented to try to correlate the experimental findings.

Of special interest are the chapters on the sleep-waking mechanism and emotions. Dr. P. Anobkin's coalescent twins serve beautifully as a test of the theories presented. It is unfortunate they did not live longer.

Dr. Miller was wise in inserting the anatomic section at the end, because many run the danger of being "floundered" by such material. Even the physiologic and clinical material is difficult to grasp at times. However, this common territory where internal medicine, neurology and research must meet is worth the closest scrutiny.

J. T.

**TRAUMA OF THE CENTRAL NERVOUS SYSTEM.** Proceedings of the Association for Research in Nervous and Mental Diseases, December 17, and 18, 1943, Pp. 679. Baltimore: Williams & Wilkins, 1945. Price, \$8.00.

THIS is the twenty-third of a series of yearly volumes in which the proceedings of the Association for Research in Nervous and Mental Disease are collected and published. The advent of the war gave impetus to many types of research, and the field of central nervous system trauma profited, as is readily seen in this collection of excellent papers by many of the outstanding men in this field.

The book may be divided into 2 separate parts: experimental and clinical. The experimental group of papers is included in the first half of the book and studies range from the mechanism and pathology of trauma to gasometric blood studies during experimental trauma. Included here is a study of the history of cranial trauma from the 17th century B.C. to 1855. The bibliography for this particular paper lists 149 references. The pathology and history of cranial trauma receives considerable attention (5 papers), and experimental methods for producing cranial trauma are discussed. One paper deals with the theory of vasoparalysis due to injury, leading to vasodilatation and hemostasis, anoxia, collection of metabolites ( $\text{CO}_2$ ), further dilatation and necrosis. Another study, based on 284 cases of cranial injury, shows that 11.5% had upper brain stem damage. The author then divides these patients into those with acute and those with subacute onset of "decompensation" or failure of vital signs and points out that while those with the acute syndrome usually die, the subacute group may be saved by prompt surgery.

The clinical group of papers takes up the remainder of this volume and deal primarily with diagnosis, prognosis, and management. About 35% of this group deals with diagnosis and includes papers on general clinical methods as well as on electro-encephalography and air studies. The electro-encephalograph has now become a practical tool for the use of the neurologist and neurosurgeon, and this study throws added light on a relatively new field, particularly in the matter of determining the severity of an injury and forecasting the probable long range result. The use of air studies—either ventriculogram or pneumo-encephalogram—in patients with acute head injuries may not meet with the approval of all neurosurgeons, but as outlined here, the value of the information thus gained may well outweigh the risks involved. The statement is made that untoward reactions as the result of ventriculography are no worse than those with brain tumors. But it must be remembered that the mortality of ventriculography is relatively high in the presence of brain tumor unless followed by operation. Discussions of post-traumatic sequelæ occupy approximately 50% of the clinical division of the volume and subjects range from

exhaustive psychologic examinations and their prognostic value to traumatic epilepsy and the advisability of surgery for its treatment.

Of value to everyone having to do with head injuries are 3 very practical articles dealing with the use of hypertonic solutions, infections, and general management of cranial traumatic cases. The first of these is easily and quickly read; the others are explicit and detailed in their discussions of techniques and methods. The most regrettable fact is that penicillin is not discussed in any detail.

The entire volume is an excellent source of reference material, not only for the laboratory worker, but for the clinician. The considerable space allocated to the discussion of post-traumatic states should make this book of especial interest to those who will be dealing with returning war casualties. It should be in the library of anyone having more than a casual interest in cranial trauma.

J. D.

**AMERICAN PHARMACY.** By twenty-two authors; editor-in-chief RUFUS A. LYMAN, M.D., Dean of the College of Pharmacy and Director of the Student Health Service, Univ. of Nebraska. Pp. 525; 197 ills. Phila.: J. B. Lippincott, 1945. Price, \$8.50.

ACCORDING to the preface, "Pharmacy is standing on the brink of the dawn of a new era which will require a broader background training in the basic sciences and a longer and more intensive study in the professional subjects for those who wish to practice or become leaders in the respective fields of specialization. American Pharmacy has been planned with these developments in mind. It has been designed not as a pharmaceutical compendium, but as a textbook, a teaching tool, for the specific purpose of better teaching. It serves the practicing pharmacist as a working tool. Part I of the text deals with the fundamental principles of the basic sciences as applied to pharmaceutical processes. Part II covers the field of pharmaceutical preparations with emphasis placed upon the processes involved in their manufacture. Part III gives the basic information about products of biological origin" (vitamins, endocrines, sera, vaccines, allergens). . . . "Special care has been taken to make it of value to the physician who has had no pharmaceutical training and is seeking the best media and methods for the administration of drugs." Part I is indeed a considerable advance in the desired direction and should be valuable to the prospective or practicing pharmacist as well as the thoughtful physician. Part II would be much more useful to the physician if it dealt less with standard official pharmaceutical preparations (about which his information is already adequate for his needs), and more with the newer synthetic and natural products and the specialties of various manufacturers (about which unbiased information is not easy for him to obtain); practical hints from experienced and disinterested pharmacists as to the best methods of using the newer vehicles, detergents and active drugs would greatly increase its value to the physician. Part III is concise and interesting and contains very useful tabular summaries of U.S.P. and N.N.R. sera, vaccines and diagnostic products, but no practically useful information about the new antibiotic agents. The writing is uniformly good, the information authoritative and references are given in each chapter. The greatest value of this book to physicians should lie in its discussion of modern detergents and other vehicles for cutaneous medication, for this information now is badly scattered.

C. S.

#### NEW BOOKS

*Essentials of Neuro-psychiatry.* A Textbook of Nervous and Mental Disorders. By DAVID M. OLKON, S.B., A.M., M.D., Associate Professor of Psychiatry, College of Medicine, University of Illinois. Pp. 310; 138 ills. Phila.: Lea & Febiger, 1945. Price, \$4.50.

*The Osseous System.* A Handbook of Roentgen Diagnosis. By VINCENT W. ARCHER, M.D., Professor of Roentgenology, University of Virginia Department of Medicine. Pp. 320; 148 figs. Chicago: Year Book Publishers, 1945.

*La Silicosis Pulmonar.* By DR. HUGO DOONER, Medico del Departamento de Higiene Industrial de La Direccion General de Sanidad Y del Hospital San Vicente, Ex Medico Del Mineral de Cobre de Potrerillos. Pp. 195. Santiago de Chile: Zig-Zag, 1944.

*The British Encyclopædia of Medical Practice*, Including Medicine, Surgery, Obstetrics, Gynæcology, and other Special Subjects. Under the General Editorship of SIR HUMPHRY ROLLESTON, Bart., G.C.V.O., K.C.B., M.D., D.Sc., F.R.C.S., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge. (A) Medical Progress, 1945. Pp. 396 and 37 pp. of Index. (B) Cumulative Supplement, 1945 (in separate board binding). Pp. 255. London: Butterworth & Co., Ltd., 1945.

THESE 2 volumes continue this useful series in the manner previously described. They are obviously not suited for a brief review.

*The Medical Clinics of North America.* Boston Number. Symposium on Specific Methods of Treatment. Pp. 1341. Phila.: W. B. Saunders, 1945. Price, \$16.00 per year.

*Endurance of Young Men.* Monograph of the Society for Research in Child Development. Vol. X, Serial No. 40, No. 1. Pp. 284. Washington: National Research Council, 1945. Price, \$2.50.

*The Way of an Investigator.* A Scientist's Experiences in Medical Research. By WALTER BRADFORD CANNON, M.D., George Higginson Professor of Physiology, Emeritus, Harvard University Medical School. Pp. 229. New York: W. W. Norton, 1945. Price, \$3.00.

*Experimental Catatonia.* A General Reaction-Form of the Central Nervous System and Its Implications for Human Pathology. By HERMAN HOLLAND DE JONG, M.D., Associate Professor of Neuro-Psychiatry, Duke University Medical School, Durham, North Carolina. Former Director of the Neurophysiological Institute, Amsterdam University, Holland. Pp. 225. Baltimore: Williams & Wilkins, 1945. Price, \$4.00.

*Les Etats de Carence en Belgique Pendant L'Occupation Allemande, 1940-1944.* By LUCIEN BRULL and others, Institut de Clinique et de Policlinique Médicales, Université de Liege. Pp. 285; frequent tables and charts. Liege Editions Soledi; and Paris: Hermann & Co., Editeurs, 1945.

THIS interesting monograph on the food and nutrition problem in Belgium during the German occupation should be of interest and value for those concerned with these subjects. The 16 articles cover clinical and statistical studies of such items as hemoglobin levels, school examinations; weight; blood pressure and serum protection in Out-patient Departments; malnutrition; hunger edema; vitamin deficiencies; osteomalacia; gastro-intestinal disorders, etc. Translation into English of the Introduction and various summaries facilitate reading for those not conversant with French.

E. K.

*Hidden Hunger.* By ICIE G. MACY, Ph.D., and HAROLD H. WILLIAMS, Ph.D., Research Laboratory Children's Fund of Michigan. Pp. 286. Lancaster: Jacques Cattell, 1945. Price, \$3.00.

*Uranium and Atomic Power.* By JACK DE MENT, Research Chemist, The Mineralogist Laboratories, and H. C. DAKE, Editor, The Mineralogist Magazine. With Appendix on the Atomic Bomb. Pp. 335. Brooklyn: Chemical Publishing Co., 1945. Price, \$4.00.

*What the Informed Citizen Needs to Know.* Edited by BRUCE BLIVEN and A. G. MEZERIK. Pp. 377. New York: Duell, Sloan and Pearce, 1945. Price, \$3.00.

*Personality in Arterial Hypertension.* By C. A. L. BINGER, and others. Pp. 228. New York: The American Society for Research in Psychosomatic Problems, 1945. Price, \$3.00.

*General and Plastic Surgery.* With Emphasis on War Injuries. By J. EASTMAN SHEEHAN, M.D., Professor of Plastic Reparative Surgery, New York Polyclinic Medical School and Hospital. Pp. 345. New York: Paul B. Hoeber, 1945. Price, \$6.75.

- Pulmonary Edema and Inflammation. An Analysis of Processes Involved in the Formation and Removal of Pulmonary Transudates and Exudates.* By CECIL K. DRINKER, M.D., D.Sc., Professor of Physiology, School of Public Health, Harvard University, Boston, Mass. The Nathalie Gray Bernard Lectures Delivered at The Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, North Carolina, in December, 1944. Pp. 106. Cambridge: Harvard University Press, 1945. Price, \$2.50.
- Virus as Organism. Evolutionary and Ecological Aspects of Some Human Virus Diseases.* By FRANK MACFARLANE BURNET, M.D., F.R.S., Director, Walter and Eliza Hall Institute of Research in Pathology and Medicine, Melbourne, Australia. Pp. 134. Cambridge: Harvard University Press, 1945. Price, \$2.00.
- Hahnemann. The Adventurous Career of a Medical Rebel.* By MARTIN GUMPERT. Pp. 251. New York: L. B. Fischer, 1945. Price, \$3.00.
- New Goals for Old Age.* Edited by GEORGE LAWTON. Pp. 210. New York: Columbia University Press, 1944. Price, \$2.75.
- What People Are. A Study of Normal Young Men.* By CLARK W. HEATH. Pp. 141. Cambridge: Harvard University Press, 1945. Price, \$2.00.
- Men, Mind and Power.* By DAVID ABRAHAMSEN, M.D., Dept. of Psychiatry, Columbia University. Pp. 155. New York: Columbia University Press, 1945. Price, \$2.00.
- Rorschach's Test. II. A Variety of Personality Pictures.* By SAMUEL J. BECK, PH.D., Head of Psychology Laboratory, Dept. of Neuropsychiatry, Michael Reese Hospital, Chicago. Foreword by ROY R. GRINKER, Lt. Col., M.C. Pp. 402. New York: Grune & Stratton, 1945. Price, \$5.00.
- Microbes of Merit.* By OTTO RAHN, Professor of Bacteriology, Cornell University. Pp. 277. Lancaster: Jacques Cattell, 1945. Price, \$4.00.
- In the Doctor's Office. The Art of Being a Medical Assistant.* By ESTHER JANE PARSONS, Formerly Research Technician, Dept. of Biochemistry, College of Physicians and Surgeons, Columbia University; Formerly Instructor in Medical Office Procedures, Paine Hall School for Medical Assistants, New York City. Pp. 295. Phila.: J. B. Lippincott, 1945. Price, \$2.00.
- Structure and Function of the Human Body.* By RALPH N. BAILLIF, PH.D., Assistant Prof. of Anatomy, Louisiana State University, School of Medicine, New Orleans, and DONALD L. KIMMEL, PH.D., Associate Professor of Anatomy, Temple University School of Medicine, Phila. Pp. 328. Phila.: J. B. Lippincott, 1945. Price, \$3.00.

## NEW EDITIONS

- The Autonomic Nervous System.* By ALBERT KUNTZ, PH.D., M.D., Professor of Micro-anatomy in St. Louis University School of Medicine. Third Ed. Pp. 687; 91 figs. Phila.: Lea & Febiger, 1945. Price, \$8.50.
- A Text-book of Neuro-anatomy.* By ALBERT KUNTZ, PH.D., M.D., Professor of Micro-anatomy in St. Louis University School of Medicine. Fourth Ed. Pp. 478; 325 figs. Phila.: Lea & Febiger, 1945. Price, \$6.50.
- Electrotherapy and Light Therapy. With the Essentials of Hydrotherapy and Mechanotherapy.* By RICHARD KOVACS, M.D., Professor of Physical Therapy, New York Polyclinic Medical School and Hospital; Attending Physical Therapist, Manhattan State, Harlem Valley State, Columbus and West Side Hospitals. Fifth Ed. Pp. 694; 352 ills. Phila.: Lea & Febiger, 1945. Price, \$8.50.
- Classic Descriptions of Disease.* By RALPH H. MAJOR, M.D., with 195 Contributors, Professor of Medicine, University of Kansas School of Medicine. Pp. 679; 158 ills. Springfield, Ill.: Charles C Thomas, 1945. Price, \$6.50.
- Manual of Psychological Medicine. For Practitioners and Students.* By A. F. TREDGOLD, M.D., F.R.S.E., Consulting Physician to University College Hospital, London. Second Ed. Pp. 308. Baltimore: Williams & Wilkins, 1945. Price, \$5.00.

*Familial Nonreaginic Food-allergy.* By ARTHUR F. COCA, M.D., Medical Director, Lederle Laboratories. Second Ed. Pp. 191. Springfield, Ill.: Charles C Thomas, 1945. Price, \$3.75.

*A Textbook of Surgery.* By JOHN HOMANS, M.D., Clinical Professor of Surgery, Emeritus. Compiled from Lectures and Other Writings of Members of the Surgical Department of The Harvard Medical School. With a Special Bibliographical Index. Sixth Ed. Pp. 1278; 530 figs. Springfield, Ill.: Charles C Thomas, 1945. Price, \$8.00.

*Physical Treatment by Movement, Manipulation and Massage.* By JAMES B. MENNELL, M.A., M.D., B.C.(Cantab.), etc., Consulting Physiotherapist, St. Thomas' Hospital and late Lecturer, Massage Training School. Fifth Ed. Pp. 512; 288 ills. Phila.: Blakiston, 1945. Price, \$7.00.

*Gould's Medical Dictionary.* Edited by C. V. BROWNLOW and Staff. Fifth Ed. Pp. 1528. Phila.: Blakiston, 1945. Price, \$7.50.

This edition was first printed in 1941. The edition which we have just received was reprinted in May, 1945. The usual amount of additions and corrections have been made. E. K.

*Textbook of Medicine.* By Various Authors. Edited by J. J. CONYBEARE, M.C., D.M., (OXON.), F.R.C.P., Physician to Guy's Hospital, London. Seventh Ed. Pp. 1165. Baltimore: Williams & Wilkins, 1945. Price, \$8.00.

*Hygiene.* By J. R. CURRIE, M.A., (OXON.), M.D., LL.D., (GLAS.), D.P.H., (BIRM.), F.R.C.P., (EDIN.), Professor-Emeritus of Public Health, University of Glasgow and A. G. MEARNES, B.Sc., M.D., B.Sc. (Public Health), D.P.H., (GLAS.), F.R.S., (EDIN.), Senior Lecturer and Lecturer-Examiner in Public Health, University of Glasgow. Second Ed. Pp. 432; 89 figs. Baltimore: Williams & Wilkins, 1945. Price, \$6.00.

#### NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMHAAER, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles, arranged alphabetically according to the name of the first author and should be complete that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

During the emergency 150 REPRINTS will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150.

#### To the Subscriber to

#### The American Journal of the Medical Sciences

Due to the increased costs of material and labor, we find it necessary to increase the subscription price of THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES to \$7.00 per annum. This is the first increase in price since 1920, when it cost \$5.00 a year, the price that was established at its origin in 1820.

The new rates, effective January 1, 1946, will be \$7.00 in the United States, in South and Central America; with \$.96 extra for postage in Canada and all other countries.

All new subscriptions and renewals for the year 1946 received with payment up to and including December 31, 1945 will be accepted at the present rate of \$6.00.

We regret the necessity of making this change in price and we shall thank you for your continued patronage.

Very truly yours,  
LEA & FEIGER,  
Publishers.

# INDEX

## A

- Addison's disease, Tiselius electrophoresis studies of plasma proteins in, 81
- Adenocarcinoma of the liver, Hemochromatosis associated with primary. A case illustrating diagnostic features, 245
- Adolescent and overweight children, Its significance in. The erythrocyte sedimentation rate in rheumatic fever, 173
- Adrenalin administration in persistent anxiety states, 281
- Albumin, hemoglobin and oxypolygelatin in the treatment of hemorrhagic shock, An evaluation of the effectiveness of globin, 808
- Amsterdam, H. J., and Grayzel, D. M., Intestinal lipodystrophy (lipophagia granulomatosis or Whipple's disease), 605
- Amytal interview, The, 125
- Anemia terminated by removal of a mediastinal tumor, Aplastic, 501 and leukopenia, with particular reference to leukopenia following radiation therapy, Possible effectiveness of the *L. casei* factor ("folic acid") concentrates on refractory, 463
- Aneurysm: Case report, Hemorrhagic telangiectasia with pulmonary artery, 76
- Angevine, D. M., Hamilton, T. R., Wallace, F. G., and Hazard, J. B., Lymph nodes in leishmaniasis, 33
- Anhydrosis, General acquired, 323
- Antagonism of local anesthetics against sulfonamides, 585
- Anti-thyroid compounds, The pharmacology and therapeutic applications of, 665
- Anxiety states, Adrenalin administration in persistent, 281
- Appendicitis, Salmonella, 517
- Arsenotherapy in cases of erythema of the 9th day, The danger of continued, 458
- Arterial tensions of carbon dioxide and oxygen on the cerebral blood flow and cerebral oxygen consumption of normal young men, The effects of alternations in the, 809
- Asthenia, Use of a simple postural test in neurocirculatory, 511
- Asthma, bronchial: Some problems in differential diagnosis, 114
- Atrial septal defect. Study of hemodynamics by the technique of right heart catheterization, 380

Atypical pneumonia is unchanged, Incidence of respiratory infections following attack by primary, 762

Austin, V. T., and Quastler, H., Idiopathic (?) hypoprothrombinemia, 491

Aycock, W. L., and Foley, G. E., An epidemiologic approach to the study of the biochemical mechanism of motor neuron disease—Landry's paralysis, 397

## B

- Bacilluria and urolithiasis, Typhoid, 591
- Bacterium necrophorum*, Human infection with, 596
- Balboni, V. G., Shapiro, I. M., and Kydd, D. M., The penetration of penicillin into joint fluid following intramuscular administration, 588
- Barnes, A. R., *see* Pruitt, R. D., 100
- Barnes, T. C., Somatic factors in electroencephalography, 132
- Barrus, D., *see* Riegel, C., 133
- Battles, M. G., *see* Starr, I., 133
- Battles, M. G., *see* Starr, I., 713
- Beerman, H., Biologic false positive reactions to the tests for syphilis, 524
- Bergler, E., Synchronization of neurotic behavior patterns, 470
- Biopsy for spreads and sections, A simple technique of sternal marrow, 630
- Bissell, G. W., The magnesium partition in hyperthyroidism. With special reference to the effect of thiouracil, 195
- Blau, M. H., Wounds of the heart, 252
- Blood transfusions, Experience with 2350 at an army general hospital in India, 623
- Brain and heart, combined acute vascular lesions of, A clinical-pathologic study of 15 cases, 732
- Brannon, E. S., Weens, H. S., and Warren, J. V., Atrial septal defect. Study of hemodynamics by the technique of right heart catheterization, 380
- Buffy coat from human blood, The relationship between cells and plasma in cultures of the, 738
- Bullitt, L., *see* Riegel, C., 133

## C

- Calcific aortic valvular stenosis, 644
- Caldwell, G. T., *see* Gill, A. J., 745
- Cameron, D. E., Adrenal in administration in persistent, anxiety states, 281
- Cancer of the mouth: Its present-day treatment, 548

- Castelnuovo, G., *see* Seager, L. D., 134  
 Cayer, D., Ruffin, J. M., and Perlzweig, W. A., Vitamin levels in sprue, 200  
 Cerebral blood flow and cerebral oxygen consumption of normal young men, The effects of alterations in the arterial tensions of carbon dioxide and oxygen on the, 809  
 Charipper, H. A., *see* Waller, R. K., 443  
 Chinese family, A heredofamilial neurologic disease, resembling Charcot-Marie-Tooth type of progressive muscular atrophy in a, 342  
 Choriocarcinoma of the testicle, 745  
 Circulation lying and standing, of tremor, and of a program of bed exercises and early rising, 1. Studies of the, 701  
 Coarctation and acute dissection of the aorta associated with pregnancy, 725  
 Comroe, J., *see* Drew, J., 810  
 Condom as a contraceptive method, The acceptability and effectiveness of the, 189  
 Congenital hemolytic anemia: A review of progress, 798  
 Contraceptive method, The acceptability and effectiveness of the condom as a, 189  
 Convalescence from surgical procedures.  
   1. Studies of the circulation lying and standing, of tremor, and of a program of bed exercises and early rising, 701  
   2. Studies of various physiologic responses to a mild exercise test, 713  
 Convalescent state, Experience with mild exercise as a test for the, 133  
 Cultures of the buffy coat from human blood, The relationship between cells and plasma in. 738
- D**
- Daft, F. S., *see* Watson, C. J., 463  
 Danowski, T. S., Man, E. B., and Winkler, A., Treatment of hyperthyroidism with a combination of iodine, thiourea in small doses, and desiccated thyroid, 777  
 Davidson, C. S., Freed, J. H., and MacDonald, H., The effect of vitamin K<sub>1</sub> oxide upon the anticoagulant properties of dicumarol, 634  
 Denhoff, E., *see* Hodge, I. G., 207  
 Derow, M. A., *see* Walker, B. S., 585  
 Deutle, R., *see* Zeidman, I., 323  
 Diabetes mellitus, The pathology of the pancreas in experimental, 381  
 Diaphragmatic flutter, Unilateral, 598  
 Dicumarol, The effect of vitamin K<sub>1</sub> oxide upon the anticoagulant properties of, 634  
 Dietary requirements for nitrogen equilibrium in the period immediately following certain major surgical operations, 133  
 Dihydrothiazole (sulfathiazoline sulfahydrothiazole), A comparison in man of sulfathiazole and 2-sulfanilyl-3-5, 775  
 Domm, A. H., *see* Flippin, H. F., 775  
 Donovan body in the yolk sac of the developing chick embryo, Report of a case with cultivation of the. Osteomyelitis caused by granuloma inguinale, 237  
 Donovan, R., *see* Rake, G., 61  
 Dowling, H. F., *see* Hirsh, H. L., 435  
 Dowling, H. F., Hirsh, H. L., The use of penicillinase in cultures of body fluids obtained from patients under treatment with penicillin, 756  
 Draper, G., Pierce, C., and Dupertuis, C. W., The relationship between cells and plasma in cultures of the buffy coat from human blood, 738  
 Drew, J., Dripps, R., and Comroe, J., The effect of morphine upon the circulatory and respiratory responses to tilting, 810  
 Dreyfuss, F., and Roth, J., Typhoid bacilluria and urolithiasis, 591  
 Dripps, R., *see* Drew, J., 810  
 Drusen (Hyaline bodies) of the optic disk, 262  
 Duff, G. L., The pathology of the pancreas in experimental diabetes mellitus, 381  
 Dungel, Nels, Rickets in Iceland, 70  
 Dupertuis, C. W., *see* Draper, G., 738
- E**
- Ebaugh, F. G., *see* Hart, W. L., 125  
 Eddy, J. H., Methionine in the treatment of toxic hepatitis, 374  
 Electrocardiographic changes associated with lesions in the deeper layers of the myocardium, 100  
   observations in normal thyroidectomized and thiourea treated rats, 443  
 Electroencephalography, Somatic factors in, 132  
 Electrophoresis studies of plasma proteins in Addison's disease, Tiselius, 81  
 Engelhardt, H. T., and Melvin, J. P., General acquired anhydrosis, 323  
 Eosinophilic lung, 238  
 Erythema of the 9th day, The danger of continued arsenotherapy in cases of, 458  
 Erythremia, Gout and subleukemic myelosis, Final note on reported case of, 638  
 Erythrocyte after splenectomy and the problems of splenic hemolysis and target cell formation, The life cycle of the, 301  
 Essex, H. E., *see* Pruitt, R. D., 100  
 Exercise test, 2. Studies of various physiologic responses to a mild, 713

## F

- Fibrocystic disease of the pancreas, 681  
 Filariasis (Bancrofti) in American soldiers, Early, 207  
 Flippin, H. F., Reinhold, J. G., Schwartz, L., and Domm, A. H., A comparison in man of sulfathiazole and 2-sulfanilyl-3-5-dihydrothiazole (sulfathiazoline sulfahydrothiazole), 775  
 Flippin, H. F., *see* Reinhold, J. G., 141  
 Flippin, H. F., *see* White, W. L., 1  
 Flippin, H. F., *see* Zintel, H. A., 421  
 Fluorine in the diet of the rat, The necessity of, 131  
 Foley, G. E., *see* Aycock, W. L., 397  
 ("Folic acid") concentrates on refractory anemia and leukopenia, with particular reference to leukopenia following radiation therapy, Possible effectiveness of the *L. casei* factor, 463  
 Forrester, J. S., *see* Machella, T. E., 38  
 Foster, W. C., *see* McClendon, J. F., 131  
 Frank, I. L., Uterine bleeding and extragenital disturbances, 787  
 Freed, J. H., *see* Davidson, C. S., 634  
 Frisch, Capt. A. W., Hemolytic transfusion reactions due to the Rh factor. Report of 2 cases, 184

## G

- Gamma globulin, A study on the prevention of mumps orchitis by, 661  
 Gaskill, H. S., *see* Kay, C. F., 342  
 Gellis, S. S., McGuinness, A. C., and Peters, M., A study on the prevention of mumps orchitis by gamma globulin, 661  
 Gellis, S. S., *see* Neefe, J. R., 561  
 Gill, A. J., Caldwell, G. T., and Goforth, J. L., Choriocarcinoma of the testicle, 745  
 Globin, albumin, hemoglobin and oxypolygelatin in the treatment of hemorrhagic shock, An evaluation of the effectiveness of, 808  
 Goforth, J. L., *see* Gill, A. J., 745  
 Goitrogen, promizole, with reference to the thyroid, metabolism and the blood, A study of the, 347  
 Granuloma inguinale, Osteomyelitis caused by. Report of a case with cultivation of the Donovan body in the yolk sac of the developing chick embryo, 237  
 Grayzel, D. M., *see* Amsterdam, H. J., 605  
 Greenblatt, A. P., *see* Greenblatt, I. J., 596  
 Greenblatt, I. J., and Greenblatt, A. P., Human infection with bacterium necrophorum, 596  
 Grigger, R. P., *see* Riegel, C., 133

## H

- Hagaman, J. B., *see* Tietze, C., 189  
 Hamilton, A., and Parkins, W., An evaluation of the effectiveness of globin, albumin, hemoglobin and oxypolygelatin in the treatment of hemorrhagic shock, 808  
 Hamilton, T. R., *see* Angevine, D. M., 33  
 Hamre, D., *see* Rake, G., 61  
 Harris, R., and Scherf, D., Unilateral diaphragmatic flutter, 598  
 Harris, T. N., The erythrocyte sedimentation rate in rheumatic fever. Its significance in adolescent and overweight children, 173  
 Hart, W. L., Ebaugh, F. G., Morgan, D. W., The amylal interview, 125  
 Hazard, J. B., *see* Angevine, D. M., 33  
 Heart catheterization, Study of hemodynamics by the technique of right. Atrial septal defect, 380  
 combined acute vascular lesions of brain and, A clinical-pathologic study of 15 cases, 732  
 Wounds of the, 252  
 Heilman, D. H., Heilman, F. R., Hinshaw, C., Nichols, D. R., and Herrell, W. E., Streptomycin: Absorption, diffusion, excretion and toxicity, 576  
 Heilman, F. R., *see* Heilman, D. H., 576  
 Hemochromatosis associated with primary adenocarcinoma of the liver. A case illustrating diagnostic features, 245  
 Hemoglobin and oxypolygelatin in the treatment of hemorrhagic shock, An evaluation of the effectiveness of globin, albumin, 808  
 Hemolysis and target cell formation, The life cycle of the erythrocyte after splenectomy and the problems of splenic, 301  
 Hemolytic anemia, Congenital: A review of progress, 798  
 Hemorrhagic shock, An evaluation of the effectiveness of globin, albumin, hemoglobin and oxypolygelatin in the treatment of, 808  
 telangiectasia with pulmonary artery aneurysm: Case report, 76  
 Henle, G., *see* Henle, W., 369  
 Henle, W., and Henle, G., Interference between inactive and active viruses of influenza: III. Cross-interference between various related and unrelated viruses, 362  
 IV. The nature of the interfering agent, 369  
 Hepatitis and infectious (epidemic) hepatitis, Homologous serum, Experimental study of immunity in volunteers. A preliminary report, 561  
 Oral administration to volunteers of feces from patients with homologous serum, 29



Hepatitis, infective, 18

Methionine in the treatment of toxic, 374

Hereditary familial neurologic disease, resembling Charcot-Marie-Tooth type of progressive muscular atrophy, in a Chinese family, A, 342

Herrell, W. E., *see* Heilman, D. H., 578

Heyman, A., *see* Sheldon, W. H., 237

Higgins, G. M., A study of the goitrogen, promizole, with reference to the thyroid, metabolism and the blood, 347

Hinshaw, H. C., *see* Heilman, D. H., 576

Hirsh, H. L., and Dowling, H. F., Observations on the continuous intramuscular method of administering penicillin, 435

Hirsh, H. L., *see* Dowling, H. F., 756

Hodes, P. J., and Wood, F. C., Eosinophilic lung, 288

Hodge, Capt. I. G., Denhoff, Capt. E., and Vander Veer, Lt. Col. J. B., Early filariasis (Bancrofti) in American soldiers, 207

Homburger, F., Effect of sodium salicylate on the sedimentation rate of erythrocytes *in vitro*, 168

Humphreys, G. H., and Southworth, H., Aplastic anemia terminated by removal of a mediastinal tumor, 501

Hydrometrocolpos in infancy—a cause of urinary retention, intestinal obstruction and edema of the lower extremities, 751

Hydroquinone and mono-methyl-*p*-aminophenol sulfate, 328

Hypersensitivity induced by penicillin, A study of the types of, 158

Hyperthyroidism, The magnesium partition in. With special reference to the effect of thiouracil, 195  
with a combination of iodine, thiourea in small doses, and desiccated thyroid, 777

Hypoprotebinemia, Idiopathic (?), 491

## I

Iceland, Rickets in, 70

Idiopathic (?) hypoprotebinemia, 491

Inductees, The xiphosternal crunch and its incidence in healthy, 333

Infection with *Bacterium necrophorum*, Human, 596

Infectious mononucleosis. An analysis of 26 clinical and 340 subclinical cases, 765

Influenza, Interference between inactive and active viruses of, 362

Interference between inactive and active viruses of influenza, 362

Intestinal lipodystrophy (lipophagia granulomatosa or Whipple's disease), 605

Intestinal obstruction and edema of the lower extremities, Hydrometrocolpos in infancy—a cause of, 751

Intramuscular method of administering penicillin, Observations on the continuous, 435

## J

Jeffers, W. A., Sheiman, S. C., and O'Brasky, G. H., Use of a simple postural test in neurocirculatory asthenia, 511

Johnson, B. B., *see* Rubenstein, A. D., 517

## K

Kavanagh, F., *see* Rake, G., 61

Kay, C. F., and Gaskill, H. S., A hereditary familial neurologic disease, resembling Charcot-Marie-Tooth type of progressive muscular atrophy, in a Chinese family, 342

Keefer, C. S., Penicillin—its present status in the treatment of infections. The Nathan Hatfield Lecture XXIX, 147

Kety, S., and Schmidt, C., The effects of alterations in the arterial tensions of carbon dioxide and oxygen on the cerebral blood flow and cerebral oxygen consumption of normal young men, 809

Kinney, T. D., Sylvester, R. E., and Levine, S. A., Coarctation and acute dissection of aorta associated with pregnancy, 725

Kirby, C. K., Experiences with 2350 blood transfusions at an army general hospital in India, 623

*Klebsiella pneumoniae* bacteremia successfully treated by penicillin, 66

Kobacker, J. L., and Mehlin, G. B., *Klebsiella pneumoniae* bacteremia successfully treated by penicillin, 66

Koerber, W. L., *see* Rake, G., 61

Koop, C. E., *see* Riegel, C., 133

Kovc, Simon, Stevens-Johnson syndrome. (Eruptive fever with stomatitis and conjunctivitis), 611

Kvale, W. F., *see* Roth, G. M., 653

Kydd, D. M., *see* Balboni, V. G., 588

## L

Lam, C. R., *see* O Neal, W. J., 181

Landry's paralysis, An epidemiologic approach to the study of the biochemical mechanism of, motor neuron disease, 397

Laryngeal edema, myocarditis and unexpected death, 296

(Laryngotracheobronchitis, Early acute), Laryngeal edema, myocarditis and unexpected death, 296

- Leifer, W., The danger of continued arsenotherapy in cases of erythema of the 9th day, 458
- Leishmaniasis, Lymph nodes in, 33
- Lembcke, P. A. and Young, L. E., Incidence of respiratory infections following attack by primary atypical pneumonia is unchanged, 762
- Leukopenia, with particular reference to leukopenia following radiation therapy, Possible effectiveness of the *L. casei* factor ("Folic acid") concentrates on refractory anemia and, 463
- Levine, S. A., *see* Kinney, T. D., 725
- Lewis, L. A., *see* McCullagh, E. P., 81
- Lilly, J., *see* Pappenheimer, J., 810
- (Lipophagia granulomatosis or Whipple's disease), Intestinal lipodystrophy, 605
- Lipodystrophy, intestinal, 605
- Lisa, J. R., *see* Race, G. A., 732
- Lockwood, J. S., *see* White, W. L., 1
- Lung, Eosinophilic, 288
- Lutterloh, C. G., *see* Vander Meer, R., 765
- Lymph nodes in leishmaniasis, 33
- M**
- MacDonald, H., *see* Davidson, C. S., 634
- Machella, T. E., and Forrester, J. S., Mite or scrub typhus, 38
- Magnesium partition in hyperthyroidism, The. With special reference to the effect of thiouracil, 195
- Man, E. B., *see* Danowski, T. S., 777
- Martin, R. F., *see* Oshlag, J. A., 245
- Mayne, W., Cancer of the mouth: Its present-day treatment, 548
- Mayock, R., *see* Starr, I., 133
- Mayock, R. L., *see* Starr, I., 701
- Mayock, R. L., *see* Starr, I., 713
- Mayor's Committee on Marihuana, Marihuana problems in the City of New York, 271
- McClendon, J. F., and Foster, W. C., The necessity of fluorine in the diet of the rat, 131
- McCullagh, E. P., and Lewis, L. A., Tiselius electrophoresis studies of plasma proteins in Addison's disease, 81
- McGuinness, A. C., *see* Gellis, S. S., 661
- McKelvey, J. L., *see* Watson, C. J., 463
- Mediastinal tumor, Aplastic anemia terminated by removal of a, 501
- Mehlin, G. B., *see* Kobacker, J. L., 66
- Melvin, J. P., Jr., *see* Engelhardt, H. T., 323
- Meningitis, Penicillin in the treatment of pneumococcal, meningococcal, streptococcal and staphylococcal, 1
- Meningococcal, streptococcal and staphylococcal meningitis, Penicillin in the treatment of pneumococcal, 1
- Mertens, Elizabeth, A simple technique of sternal marrow biopsy for spreads and sections, 630
- Metabolic rate in hospitalized patients, A study of the relationship of the basal body temperature to the basal, 453
- Methionine in the treatment of toxic hepatitis, 374
- Microcrystalline sulfadiazine with that of ordinary sulfadiazine in man, A comparison of the behavior of, 141
- Millikan, G., *see* Pappenheimer, J., 810
- Mono-methyl-paraminophenol sulfate, Poisoning by, 328
- Mononucleosis, Infectious. An analysis of 26 clinical and 340 subclinical cases, 765
- Morgan, D. W., *see* Hart, W. L., 125
- Morphine upon the circulatory and respiratory responses to tilting, The effect of, 810
- Morris, P., Hydrometrocolpos in infancy—a cause of urinary retention, intestinal obstruction and edema of the lower extremities, 751
- Moses, C., A study of the relationship of the basal body temperature to the basal metabolic rate in hospitalized patients, 453
- Motor neuron disease—Landry's paralysis, An epidemiologic approach to the study of the biochemical mechanism of, 397
- Mumps orchitis, A study on the prevention by gamma globulin, 661
- Murphy, F. D., *see* White, W. L., 1
- Muscular atrophy, in a Chinese family, A hereditary familial neurologic disease, resembling Charcot-Marie-Tooth type of progressive, 342
- Myocarditis and unexpected death, Laryngeal edema, 296
- Myocardium, Electrocardiographic changes associated with lesions in the deeper layers of the, 100
- N**
- Neefe, J. R., Stokes, J., Jr., and Gellis, S. S., Homologous serum hepatitis and infectious (epidemic) hepatitis. Experimental study of immunity and cross immunity in volunteers. A preliminary report, 561
- Neefe, J. R., Stokes, J., Jr., and Reinhold, J. G., Oral administration to volunteers of feces from patients with homologous serum hepatitis and infectious (epidemic) hepatitis, 29
- Neurocirculatory asthenia, Use of a simple postural test, 511
- Neurotic behavior patterns, Synchronization of, 470
- Nichols, A. C., *see* Zintel, H. A., 421
- Nichols, D. R., *see* Heilman, D. H., 576
- Nitrogen equilibrium in the period immediately following certain major surgical operations, Dietary requirements for, 133

## O

- O'Brasky, G. H., *see* Jeffers, W. A., 511  
 Oneal, W. J., and Lam, C. R., Experiments on components A and B (Quick) of prothrombin, 181  
 Optic disk, Drusen (Hyaline bodies) of the, 262  
 Orchitis by gamma globulin, A study on the prevention of mumps, 661  
 Oshlag, J. A., and Martin, R. F., Hemochromatosis associated with primary adenocarcinoma of the liver. A case illustrating diagnostic features, 245  
 Osteomyelitis caused by granuloma inguinale. Report of a case with cultivation of the Donovan body in the yolk sac of the developing chick embryo, 237  
 Otto, T. O., *see* Washburn, R. N., 640  
 Oxypolygelatin in the treatment of hemorrhagic shock, An evaluation of the effectiveness of globin, albumin, hemoglobin, 808

## P

- Pancreas, Fibrocystic disease of the, 681 in experimental diabetes mellitus, The pathology of the, 381  
 Pappenheimer, J., Lilly, J., and Millikan, G., Respiratory flow rates and the design of oxygen equipment, 810  
 Parkins, W., *see* Hamilton, A., 808  
 Pediatrics: Congenital hemolytic anemia: A review of progress, 798  
 Penicillin, A study of the types of hypersensitivity induced by, 158  
   Case of *Streptococcus viridans* pneumonia successfully treated with, 431 in the treatment of pneumococcal, meningococcal, streptococcal and staphylococcal meningitis, 1  
   into joint fluid following intramuscular administration, The penetration of, 588  
   —its present status in the treatment of infections. The Nathan Hatfield Lecture XXIX, 147  
*Klebsiella pneumoniae* bacteremia successfully treated by, 66  
   Observations on the continuous intramuscular method of administering, 435  
 Penicillinase in cultures of body fluids obtained from patients under treatment with penicillin, The use of, 756  
 Periarthritis nodosa. A case with autopsy, 640  
 Perlzweig, W. A., *see* Cayer, D., 200  
 Peters, M., *see* Gellis, S. S., 661  
 Pheochromocytoma, A tentative test for, 653  
 Phillips, F. J., *see* Reinhold, J. G., 141  
 Pierce, C., *see* Draper, G., 738  
 Pilot, J., *see* Vander Meer, R., 765

- Plasma proteins in Addison's disease, Tiselius electrophoresis studies of, 81  
 Pneumococcal, meningococcal, streptococcal and staphylococcal meningitis, Penicillin in the treatment of, 1  
 Pneumonia is unchanged, Incidence of respiratory infections following attack by primary atypical, 762  
   successfully treated with penicillin, Case of *Streptococcus viridans*, 431  
   Tularemia. Review of American Literature and report of 15 additional cases, 223  
 Proceedings of the Physiological Society of Philadelphia, 131, 808  
 Promizole, with reference to the thyroid, metabolism and the blood, A study of the goitrogen, 347  
 Proteinuria in young men, The incidence, causes and intermittency of, 86  
 Prothrombin, Experiments on components A and B (Quick) of, 181  
 Pruitt, R. D., Barnes, A. R., and Essex, H. E., Electrocardiographic changes associated with lesions in the deeper layers of the myocardium, 100  
 Psychiatric program, A recorded. Pro-test, 782  
 Pugh, D. G., Fibrocystic disease of the pancreas, 681  
 Pullen, R. L., *see* Stuart, B. M., 223

## Q

- Quastler, H., *see* Austin, V. T., 491

## R

- Race, G. A., and Lisa, J. R., Combined acute vascular lesions of brain and heart. A clinical-pathologic study of 15 cases, 732  
 Radiation therapy, Possible effectiveness of the *L. casei* factor ("Folic acid") concentrates on refractory anemia and leukopenia, with particular reference to leukopenia following, 463  
 Rake, G., Hamre, D., Kavanagh, F., Koerber, W. L., and Donovan, R., on the toxicity of streptothricin, 61  
 Reifenshtein, G. H., Final note on a reported case of erythremia, gout and subleukemic myelosis, 638  
 Reinhold, J. G., *see* Flippin, H. F., 775  
 Reinhold, J. G., Phillips, F. J., and Flippin, H. F., A comparison of the behavior of microcrystalline sulfadiazine with that of ordinary sulfadiazine in man, 141  
 Reinhold, J. G., *see* Neefe, J. R., 29  
 Rennie, J. B., Infective hepatitis, 18  
 Respiratory flow rates and the design of oxygen equipment, 810  
   infections following attack by primary atypical pneumonia is unchanged, Incidence of, 762

Respiratory responses to tilting, The effect of morphine upon the circulatory and, 810

*Reviews* (Reviewer's initials in parentheses):

- Alexander, J., Colloid Chemistry (S. G.), 691  
 Bartlett, F. H., Infants and Children (I. W.), 271  
 Bennett, H. (Editor), The Chemical Formulary (S. G.), 694  
 Brock, Samuel, The Basis of Clinical Neurology (A. O.), 276  
 Bunnell, S., Surgery of the Hand (H. Z.), 697  
 Burch, G., A Primer of Electrocardiography (C. W.), 813  
 Clark, C., Facial and Body Prosthesis (R. I.), 817  
 Clement, F., Nitrous Oxide-Oxygen Anesthesia (R. D.), 697  
 Clendening, L., The Human Body (W. J.), 690  
 Cowan, A., Refraction of the Eye (F. A.), 557  
 Craig, Charles F., The Etiology, Diagnosis, and Treatment of Amebiasis (H. R.), 137  
 Craig, C., and Faust, E., Clinical Parasitology (I. W.), 814  
 Crutcher, H. B., Foster Home Care of Mental Patients (N. Y.), 273  
 Dalldorf, G., The Avitaminoses (E. W.), 691  
 De Kruif, P., The Male Hormone (E. K.), 278  
 Deutsch, H., The Psychology of Women (D. M.), 556  
 Feldman, M., Clinical Roentgenology of the Digestive Tract (E. P.), 269  
 Fishbein, M., Doctors at War (E. K.), 558  
 Fishbein, Morris, Common Ailments of Man (E. K.), 277  
 Flagg, P., The Art of Resuscitation (R. D.), 696  
 Ford, Frank R., Diseases of the Nervous System in Infancy, Childhood and Adolescence (I. W.), 272  
 French, H. (Editor), An Index of Differential Diagnosis of Main Symptoms (J. F.), 694  
 Fulton, J. F., A Bibliography of Visual Literature (F. A.), 558  
 Geschickter, C., Diseases of the Breast (D. C.), 692  
 Goldmann, F., Public Medical Care (G. R.), 688  
 Grant, J., and Cates, H., A Handbook for Dissectors (J. P.), 815  
 Greenblatt, R. B., Office Endocrinology (D. M.), 556  
 Grinker, R. R., Men Under Stress (N. Y.), 277  
 Haworth, N., and MacDonald, E., Theory of Occupational Therapy (C. W.), 693  
 Herrmann, G., Clinical Case Taking (J. M.), 816  
 Herrell, W. E., Penicillin and Other Antibiotic Agents (W. J.), 688  
 Hilleboe, H. E., Mass Radiography of the Chest (E. P.), 270  
 Jordan, E., Textbook of Bacteriology (J. F.), 813  
 Judovich, B., and Bates, W., Segmental Neuralgia in Painful Syndromes (R. D.), 693  
 Karnosh, L. J., A Handbook of Psychiatry (N. Y.), 557  
 Keys, T., The History of Surgical Anesthesia (E. K.), 690  
 Kolmer, J. A., Penicillin Therapy (R. M.), 270  
 Letheby, Sir Henry, A Synopsis of Medicine (E. K.), 279  
 Luck, J., and Smith, J., Annual Review of Biochemistry (D. D.), 691  
 Lyman, R., American Pharmacy (C. S.), 819  
 Mackie, T. J., and McCartney, J. E., Handbook of Practical Bacteriology (H. M.), 557  
 Mackie, T. T., Manual of Tropical Medicine (H. R.), 135  
 Maher, F. T., The Reticulo-endothelial System in Sulfonamide Activity (C. S.), 275  
 McClain, M. E., Student's Guide in Nursing Arts (L. S.), 698

*Reviews* (Reviewer's initials in parentheses):

- McCormick, C. O., Pathology of Labor, The Puerperium and the Newborn (D. M.), 137  
 Medical Clinics of North America, Chicago Number, January, 1945 (J. T.), 275  
 Medical Clinics of North America, Symposium on New Developments in Medicine (J. W.), 556  
 Medical Clinics of North America, July, 1945, Mayo Clinic No., Symposium on Medical Emergencies (J. F.), 697  
 Menninger, K. A., The Human Mind (N. Y.), 275  
 Miller, H., Central Autonomic Regulations in Health and Disease, With Special Reference to the Hypothalamus (J. T.), 818  
 Miles, W., Science in Progress (I. W.), 813  
 Minnitt, R., and Gillies, J., Textbook of Anesthetics (R. D.), 695  
 Monsarrat, K. W., Thoughts, Deeds and Human Happiness (N. Y.), 557  
 Moore, R. A., Ageing and Degenerative Diseases (E. K.), 555  
 Moulton, F. R. (Edited by), The Chemistry and Physiology of Hormones (I. Z.), 139  
 Mustard, H., Government in Public Health (G. R.), 816  
 National Research Council, by Subcommittee on Anesthesia of Division of Medical Sciences, Fundamentals of Anesthesia (R. D.), 697  
 Neisser, A., On Modern Syphilotherapy With Particular Reference to Salvarsan (H. B.), 136  
 Nissen, R., Duodenal and Jejunal Peptic Ulcer (R. P.), 138  
 Noyes, W., The Photochemistry of Gases (D. D.), 817  
 Olmsted, J. M. D., François Magendie (E. K.), 278  
 Piney, A., Clinical Atlas of Blood Diseases (E. K.), 278  
 Pinner, M., Pulmonary Tuberculosis in the Adult (M. L.), 696  
 Rogers, Sir Leonard, Tropical Medicine (H. R.), 136  
 Russell, W. L., The New York Hospital (E. K.), 138  
 Sadler, W. S., Modern Psychiatry (N. Y.), 274  
 Sahyun, M., Outline of the Amino Acids and Proteins (H. V.), 136  
 Sargent, W., An Introduction to Somatic Methods of Treatment in Psychiatry (E. B.), 135  
 Scheinfeld, A., Women and Men (E. K.), 138  
 Sevag, M. G., Immuno-catalysis (S. G.), 273  
 Stander, H., Textbook of Obstetrics (D. M.), 812  
 Stern, R., Trauma in Internal Diseases (W. S.), 689  
 Stone, E. L., The New-born Infant (I. W.), 271  
 Strecker, E., and Appel, K., Psychiatry in Modern Warfare (N. Y.), 695  
 Taylor, H., The Abortion Problem (D. M.), 692  
 Thienes, C. H., Fundamentals of Pharmacology (S. K.), 276  
 Thom, C., A Manual of the Aspergilli (F. W.), 814  
 Titus, P., The Management of Obstetric Difficulties (D. M.), 556  
 Trauma of the Central Nervous System, Proceedings of the Assn. for Research in Nervous and Mental Diseases (J. D.), 818  
 Trease, G., A Text-book of Pharmacognosy (C. S.), 813  
 Turner, C., and McHose, E., Effective Living (E. K.), 689  
 Vasconcelos, E., Modern Methods of Amputation (H. Z.), 696  
 Waite, F., The Story of a Country Medical College (E. K.), 690  
 Waksman, S. A., Microbial Antagonisms and Antibiotic Substances (H. M.), 274

*Reviews* (Reviewer's initials in parentheses):

- Walshe, F., *Diseases of the Nervous System* (J. T.), 698  
 Wartenberg, R., *The Examination of Reflexes* (A. O.), 272  
 Weil, A., *Textbook of Neuropathology* (A. O.), 276  
 Wohl, M. (Edited by), *Dietotherapy, Clinical Application of Modern Nutrition* (W. J.), 689
- Rheumatic fever, The erythrocyte sedimentation rate in the significance in adolescent and ..... 173
- Rh factor, Hemolytic transfusion reactions due to the. Report of 2 cases, 184
- Rhoads, J. E., *see* Riegel, C., 133  
 Rhoads, J. E., *see* Zintel, H. A., 421
- Rickets in Iceland, 70
- Riegel, C., Rhoads, J. E., Koop, C. E., Grigger, R. P., Bullitt, L., and Barrus, D., Dietary requirements for nitrogen equilibrium in the period immediately following certain major surgical operations, 133
- Riker, W. F., and Wescoe, W. C., The ..... and therapeutic:applied compounds, 665
- Rosner, A. A., *Protest. A recorded psychiatric program*, 782
- Rostenberg, A., and Welch, H., A study of the types of hypersensitivity induced by penicillin, 158
- Roth, G. M., and Kvale, W. F., a tentative test for pheochromocytoma, 653
- Roth, J., *see* Dreyfuss, F., 591
- Rubenstein, A. D., and Johnson, B. B., *Salmonella appendicitis*, 517
- Ruffin, J. M., *see* Cayer, D., 200
- Rundles, R. W., Hemorrhagic telangiectasia with pulmonary artery aneurysm: Case report, 76
- S**
- Salicylate on the sedimentation rate of erythrocytes *in vitro*, Effect of sodium, 168
- Salmonella appendicitis, 517
- Saphir, Otto, Laryngeal edema, myocarditis and unexpected death (Early acute laryngotracheobronchitis), 296
- Scherf, D., *see* Harris, R., 598
- Schmidt, C., *see* Kety, S., 809
- Schwartz, L., *see* Flippin, H. F., 775
- Seager, L. D., Wells, G. R., and Castelnovo, G., The effect of ultra-violet irradiation on the toxicity and chemotherapeutic action of stilbamidine, 134
- Sebrell, W. H., *see* Watson, C. J., 463
- Sedimentation rate in rheumatic fever, The erythrocyte. Its significance in adolescent and overweight children, 173  
 of erythrocytes *in vitro*, Effect of sodium salicylate on the, 168
- Septal defect, Atrial. Study of hemodynamics by the technique of right heart catheterization, 380
- Shapiro, I. M., *see* Balboni, V. G., 538
- Sheiman, S. C., *see* Jeffers, W. A., 511
- Sheldon, W. H., Thebaut, B. R., Heyman, A., and Wall, M. J., Osteomyelitis caused by granuloma inguinale. Report of a case with cultivation of the Donovan body in the yolk sac of the developing chick embryo, 238
- Shock, An evaluation of the effectiveness of globin, albumin, hemoglobin and oxypolygelatin in the treatment of hemorrhagic shock, 808
- Singer, Karl, and Weisz, Leo, The life cycle of the erythrocyte after splenectomy and the problems of splenic hemolysis and target cell formation, 301
- Sodeman, W. A., Bronchial asthma: Some problems in differential diagnosis, 114
- Solis-Cohen, Myer, The xiphosternal crunch and its incidence in healthy inductees, 333
- Solomon, S., Case of *Streptococcus viridans* pneumonia successfully treated with penicillin, 431
- Somatic factors in electroencephalography, 132
- Sophian, L. H., Calcific aortic valvular stenosis, 644
- Southworth, H., *see* Humphreys, G. H., 501
- Splenectomy and the problems of splenic hemolysis and target cell formation, The life cycle of the erythrocyte after, 301
- Sprue, Vitamin levels in, 200
- Staphylococcal meningitis, Penicillin in the treatment of pneumococcal, meningococcal, streptococcal and, 1
- Starr, I., and Mayock, R. L., Convalescence from surgical procedures. 1. Studies of the circulation lying and standing, of tremor, and of a program of bed exercises and early rising, 701
- Starr, I., Mayock, R. L., and Battles, M. G., Convalescence from surgical procedures. 2. Studies of various physiologic responses to a mild exercise test, 713
- Starr, I., Mayock, R. L., and Battles, M. G., Experience with mild exercise as a test for the convalescent state, 133
- Stenosis, Calcific aortic valvular, 644
- Sternal marrow biopsy, Simple technique for spreads and sections, 630
- Stilbamidine, The effect of ultra-violet irradiation on the toxicity and chemotherapeutic action of, 134
- Stokes, J., *see* Neefe, J. R., 29
- Stokes, J., *see* Neefe, J. R., 561
- (Stomatitis and conjunctivitis, Eruptive fever with), Stevens-Johnson syndrome, 611

- Streptococcal and staphylococcal meningitis, Penicillin in the treatment of pneumococcal, meningococcal, 1
- Streptococcus viridans* pneumonia successfully treated with penicillin, Case of, 431
- Streptomycin; absorption diffusion, excretion and toxicity, 576  
in man, Studies on. I. Absorption, distribution, excretion and toxicity, 421
- Streptothricin, On the toxicity of, 61
- Stuart, B. M., and Pullen, R. L., Tularemic pneumonia. Review of American literature and report of 15 additional cases, 223
- Sulfadiazine with that of ordinary sulfadiazine in man, A comparison of the behavior of microcrystalline, 141  
(Sulfahydrothiazole), A comparison in man of sulfathiazole and 2-sulfanilyl-3-5-dihydrothiazole (sulfathiazoline), 775
- Sulfanilyl-3-5-dihydrothiazole (sulfathiazoline sulfahydrothiazole), A comparison in man of sulfathiazole and 2-, 775
- Sulfathiazole and 2-sulfanilyl-3-5-dihydrothiazole (sulfathiazoline, sulfahydrothiazole), A comparison in man of, 775
- Sulfonamides, Antagonism of local anesthetics against, 585
- Surgical procedures, convalescence from.  
1. Studies of the circulation lying and standing, of tremor, and of a program of bed exercises and early rising, 701  
2. Studies of various physiologic responses to a mild exercise test, 713
- Sylvester, R. E., *see* Kinney, T. D., 725
- Syndrome, Stevens-Johnson, (Eruptive fever with stomatitis and conjunctivitis), 611
- Syphilis, Biologic false positive reactions to the tests for, 524
- T**
- Target cell formation, The life cycle of the erythrocyte after splenectomy and the problems of splenic hemolysis and, 301
- Telangiectasia with pulmonary artery aneurysm: Case report, Hemorrhagic, 76
- Testicle, Choriocarcinoma of the, 745
- Thebaut, B. R., *see* Sheldon, W. H., 238
- Thiouacil, With special reference to the effect of. The magnesium partition in hyperthyroidism, 195
- Thiourea in small doses, and desiccated thyroid, Treatment of hyperthyroidism with a combination of iodine, 777  
treated rats, Electrocardiographic observations in normal thyroidectomized and, 443
- Thyroidectomized and thiourea treated rats, Electrocardiographic observations in normal, 443
- Thyroid, metabolism and the blood, A study of the goitrogen, promizole, with reference to the, 347  
treatment of hyperthyroidism with a combination of iodine, thiourea in small doses, and desiccated, 777
- Tietze, C., and Hagaman, J. B., The acceptability and effectiveness of the condom as a contraceptive method, 189
- Transfusion reactions due to the Rh factor. Report of 2 cases, Hemolytic, 184
- Tularemic pneumonia. Review of American literature and report of 15 additional cases, 223
- Typhoid bacilluria and urolithiasis, 591
- Typhus, mite or scrub, 38
- U**
- Ultra-violet irradiation on the toxicity and chemotherapeutic action of stilbamidine, The effect of, 134
- Unilateral diaphragmatic flutter, 598
- Urinary retention, intestinal obstruction and edema of the lower extremities, Hydrometrocolpos in infancy—a cause of, 751
- Urolithiasis, Typhoid bacilluria, 591
- Uterine bleeding and extragenital disturbances, 787
- V**
- Vander Meer, R., Lutterloh, C. H., and Pilot, Jean, Infectious mononucleosis. An analysis of 26 clinical and 340 sub-clinical cases, 765
- Vander Veer, J. B., *see* Hodge, I. G., 207
- Vitamin levels in spruce, 200  
K<sub>1</sub> oxide upon the anticoagulant properties of dicumarol, The effect of, 634
- W**
- Wagener, H. P., Drusen (hyaline bodies) of the optic disk, 262
- Walker, B. S., and Derow, M. A., The antagonism of local anesthetics against the sulfonamides, 585
- Wall, M. J., *see* Sheldon, W. H., 237
- Wallace, F. G., *see* Angevine, D. M., 33
- Waller, R. K., and Charipper, H. A., Electrocardiographic observations in normal thyroidectomized and thiourea treated rats, 443
- Warren, J. V., *see* Brannon, E. S., 380
- Washburn, R. N., and Otto, T. O., Periarthritis nodosa. A case with autopsy, 640

- Watson, C. J., Sebrell, W. H., McKelvey, J. L., and Daft, F. S., Possible effectiveness of the *L. casei* factor ("Folic acid") concentrates on refractory anemia and leukopenia, with particular reference to leukopenia following radiation therapy, 463
- Weens, H. S., *see* Brannon, E. S., 380
- Weisz, Leo, *see* Singer, Karl, 301
- Welch, H., *see* Rostenberg, A., 158
- Wells, G. R., *see* Seager, L. D., 134
- Wescoc, W. C., *see* Riker, W. F., 665
- White, W. L., Murphy, F. D., Lockwood, J. S., and Flippin, H. F., Penicillin in the treatment of pneumococcal, meningococcal, streptococcal and staphylococcal meningitis, 1
- Wiley, M. M., *see* Zintel, H. A., 421
- Winkler, A. W., *see* Danowski, T. S., 777
- Wolman, I. J., The incidence, causes and intermittency of proteinuria in young men, 86
- Wood, F. C., *see* Hodes, P. J., 288

Xiphosternal crunch and its incidence in healthy inductees, The, 333

Young, L. E., *see* Lembecke, P. A., 762

Zeidman, I., and Deutle, R., Poisoning by hydroquinone and mono-methyl-  
paraminophenol sulfate, 328

Zintel, H. A., Flippin, H. F., Nichols, A. C., Wiley, M. M., and Rhoads, J. E., Studies on streptomycin in man. I. Absorption, distribution, excretion and toxicity, 421

